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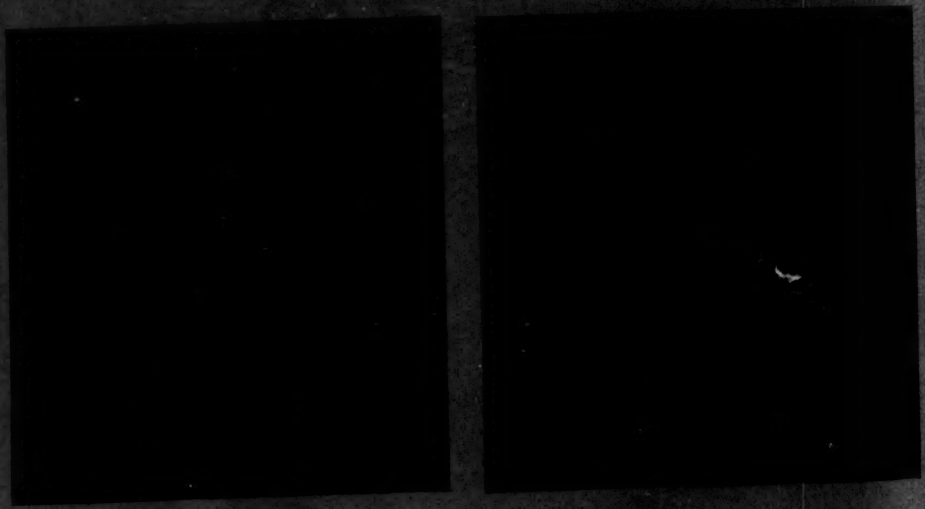

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COMMUNICATIONS

THE NERVOUS SYSTEM IN VISUAL ADAPTATION*

BY

L. C. THOMSON

From the Vision Research Unit, Institute of Ophthalmology, London

DURING the course of the day the light intensity varies widely, and the human visual mechanism is able to alter its sensitivity to light to suit the prevailing conditions. At night the eye may be as much as 10,000 times more sensitive to light than it is during the day.

Opinion as to the nature of this adaptation mechanism is divided into two main groups:—

1. That which asserts with Hecht (1920, etc.) and his pupils that adaptation is entirely a photochemical phenomenon, the sensitivity changes being wholly explained by the bleaching and regeneration of light sensitive pigments.

2. That which maintains that there is, as well as the photochemical adaptation, some change in the sensitivity of the nervous apparatus.

Broadly, the photochemical idea is that during light adaptation

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visual purple and other visual pigments are bleached with the formation of products which are not sensitive to light. Bleaching lowers the concentration of sensitive material in the retina, and, in consequence, the sensitivity of the mechanism to light. The recovery of sensitivity in the dark is due to the resynthesis of the sensitive material from its photo-products. The absolute threshold light energy as measured during dark adaptation is some simple function of the concentration of this sensitive material in the retina.

Hecht and his pupils do not admit any change in the sensitivity of the nervous apparatus during adaptation; receptors, retinal synapses, optic nerve fibres, lateral geniculate bodies, etc., are merely the means by which the state of affairs in the photochemical system is relayed to the brain.

It is, of course, admitted that the state of the nervous system can influence the value obtained for the threshold energy during dark adaptation. The subject may be under the influence of drugs, or inattentive, or breathing air deficient in oxygen, so that in each case the light energy required to evoke a threshold sensation will probably differ from normal. What is not admitted is that sensitivity changes in the nervous system can occur in response to alterations in the light stimulus at the eye.

Mandelbaum (1941) states the " photochemical " point of view as follows: " Dark adaptation according to classic photochemical concepts reflects simply the regeneration of the photo-sensitive pigments in the rod and cone cells; it is purely a retinal phenomenon and is confined to the sentient cells. This view is not universally accepted to-day. Although the bleaching and regeneration of visual purple are so easily demonstrated and so obviously a part of the visual mechanism, some assign it to a secondary position; others supplement this mechanism with various hypothetic nerve mechanisms, all of which are vague and for which there is no evidence."

Crawford (1946) also states: " . . . it has not so far been found necessary to introduce any component of recovery due to the nervous transmission to the brain. The quantitative explanation depends largely on the theory of the kinetics of chemical reactions . . . "

The " photochemical " explanation has somewhat eclipsed any other view and an attempt is made to present below some of the evidence in favour of a nervous component to adaptation.

" Photochemical " Theories of Visual Adaptation.—It is sometimes argued that a " photochemical " theory of adaptation (Hecht, 1929 and 1937, for instance) leaves no room for nervous adaptational changes (Mandelbaum, 1941) and it is essential to see how far this may be true.

Hecht's theory can be stated qualitatively in symbols thus :—

$$\text{Light} \longrightarrow \left[S \underset{\text{dark}}{\overset{\text{light}}{\rightleftharpoons}} P+A; \qquad L \parallel P+A \parallel \rightarrow I \right] \longrightarrow \text{Impulse}$$

This means that when light strikes the retina, a photochemical substance, S, is split into two photo-products, P and A. Freshly formed P and A, indicated by $\| P + A \|$, catalyses a further non-light sensitive reaction ($L \rightarrow T$) which results in the formation from the inactive substance (L) of an active substance (T) which initiates the nerve impulse. In addition, P and A combine in the dark to reform the sensitive material, S. This reaction, together with the photochemical breakdown, forms the basis of the sensitivity changes during light and dark adaptation.

The theory is based firstly upon experimental work with various invertebrates, such as the clam *Mya Arenaria*, which are sensitive to light and react by a motor response, the contraction of the syphon; secondly, upon the application of a knowledge of the kinetical behaviour of simple chemical reactions to the experimental results of both human and invertebrate experiments.

When *Mya* is illuminated continuously, it at first reacts by a strong contraction of its syphon, then as light adaptation proceeds, the syphon relaxes and the animal is less sensitive to light. In darkness the animal recovers its sensitivity, which recovery may be measured by determining the reaction of time to a dim test light of constant intensity.

In his final analysis for *Mya*, Hecht assumes that at all stages of dark adaptation a constant quantity of the photoproducts, P and A, freshly formed during stimulation by the test light, is required to produce a reaction in the syphon; and states that the velocity with which P and A are produced during this test light stimulation is proportional to the concentration of the sensitive material, S, present in the retina at that moment.

Hecht's theory may be illustrated graphically (Fig. 1, overleaf). In this diagram the time taken by the test light to produce P and A is represented on the abscissa, the quantity of photoproduct formed is on the ordinate, and the constant amount of P and A required at all stages of dark adaptation to stimulate the receptors is represented by the line XY. Early in dark adaptation this line is reached slowly, via OY, which results in the period, t_1, which together with a latent period of constant duration makes up the reaction time. Later, when the sensitive material has been allowed to accumulate, the line XY is reached more rapidly, via OZ when the test light is applied, which results in the shorter period, t_2, and a shorter reaction time.

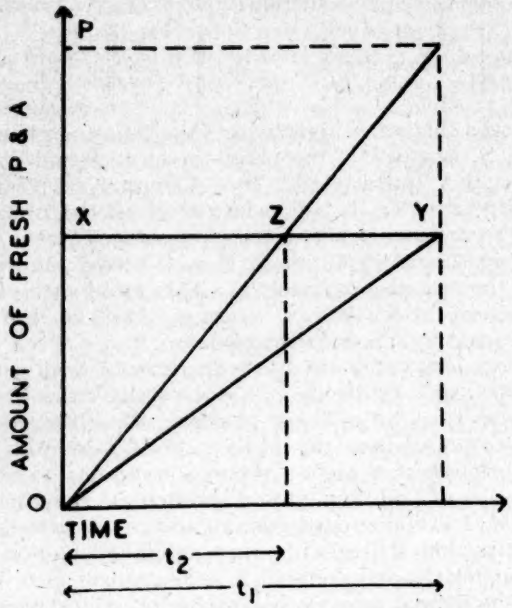


FIG. 1.—Diagram to illustrate Hecht's "photochemical" explanation of adaptation in the visual mechanism.

Thus the values of the periods, t_1 and t_2, and the values of the whole reaction time, should yield information about the way in which the sensitive material, S, regenerates in the retina, and Hecht finds that a hyperbola, which also describes the course of a bimolecular chemical reaction, can be constructed and fitted to the experimental determinations of the reaction time. Since this curve fitted the data within the experimental error, Hecht concluded that two substances, P and A, were recombining during dark adaptation to form the sensitive material, S, a conclusion which is not entirely justified.

Now it is clear that although the rate of photochemical decomposition may vary with the concentration of the photosensitive pigment, i.e., the slope of the line OY may alter, the variation may be insufficient to account for the whole of the sensitivity change during dark adaptation. The amount of freshly formed products required to stimulate the receptors may also vary during dark adaptation, this amount being larger at the beginning and smaller towards the end. This would mean that the sensitivity change is partly due to a change in behaviour of the receptors, and

that, in Fig. 1, the long period, t_1, results from the need for the test light to form the larger quantity of photoproducts, OP, before impulses are generated in the receptors. In the shorter period, t_2, which is found in the later stages of dark adaptation, only the amount OX, is required to stimulate the receptors, because they are then more sensitive to freshly formed photoproducts. The dark adaptation measurements should now describe to some extent the recovery of the sensitivity of the receptor part of the nervous apparatus.

Indeed, Hecht's hypothesis is merely one of many which might have been chosen. Hecht was aware of the difficulty of choosing between " photochemical " hypotheses on the basis of the above dark adaptation measurements alone (1923), and he makes his choice between the first of those stated above and yet another hypothesis, by consulting the behaviour of *Mya* when the animal is brought to various steady states of light adaptation.

The difficulty is further emphasised when the data from human subjective experiments is considered. Here Hecht (1920; 1921; 1929) has had to make a further assumption (as Houstoun, 1930, has pointed out) to relate the concentration of the photosensitive substances to the measurements, because the ordinates are now no longer reaction time, but the logarithm of the threshold energy required to produce a minimum sensation. The assumption made is that the concentration of sensitive material present in the retina at any moment during dark adaptation is inversely proportional to the logarithm of the threshold energy necessary to evoke the minimum sensation of light. Once again a " bimolecular " curve was derived and was found to fit the data if the rod and cone portions of the results were treated separately. On the other hand the data could easily be explained as for *Mya*, by assuming that the amount of photoproduct required to stimulate the receptors was not a constant, and that the threshold curve describes the recovery of sensitivity of the receptors. Such an explanation might be the better if it proved to be supported by other evidence.

Hecht's theory does not, therefore, exclude a nervous explanation for adaptation. Indeed, such a theory which rests merely upon the goodness-of-fit between certain derived curves and the experimental results, could hardly be conclusive without some further support. The fact that a hyperbola describes both a bimolecular chemical reaction and the behaviour of the reaction time during the dark adaptation of *Mya* does not entitle one to link these two phenomena as cause and effect. They may only be phenomena which are describable in the same mathematical language and require other evidence to forge the link

between them. It is a matter of some doubt as to whether the evidence from other visual measurements is adequate to support Hecht's theory as a whole.

Lythgoe's Discrepancy.—Numerous objections have been raised to Hecht's entirely photochemical explanation of visual adaptation (see, for instance, Lythgoe, 1940; Granit, 1947; Elsberg and Spotnitz, 1938).

Lythgoe (1940) pointed out that there is a large discrepancy between the magnitude of the change in concentration of photosensitive material and the change in the sensitivity of the visual mechanism during dark adaptation. On the basis of Hecht's views, if the concentration of the photosensitive material was to increase in the retina by a factor of two, the sensitivity of the visual mechanism should also be doubled. Actually, as Lythgoe points out, this does not fit the facts. If one assumes that Granit's figures for visual purple accumulation in the cat's retina apply to man, and then considers the rod section only of the human dark adaptation threshold curve, the visual purple approximately doubles its concentration between the 7th and 30th min. of dark adaptation. This is associated with a 1,000-fold increase in sensitivity and the visual purple increase is thus not nearly enough to account for the sensitivity increase.

One explanation for this discrepancy might well be that during the course of dark adaptation the receptors become 500-fold more sensitive to the products of the photochemical mechanism. If this were so, visual adaptation would be largely a nervous phenomenon.

Lythgoe was impressed, too, by the gradual reduction in the ability of the eye to perform the finer visual judgments as the sensitivity increased in the dark, and to harmonize these two effects he postulates that in the dark adapted eye there is a greater amount of nervous intercommunication in the synaptic layers of the retina.

Such a synaptic " switching " would account quite well for the discrepancy between visual purple accumulation and sensitivity increase.

The Shape of the Recovery Curves.—A further objection which has been raised by a number of authors (Winsor and Clark, 1936; Lythgoe, 1940; Wright, 1946) is that dark adaptation recovery curves following various degrees of light adaptation do not retrace one another's paths.

Consider two experiments, 1 and 2, where the light adaptation in 1 is greater than in 2. On the basis of Hecht's idea, $S \rightleftharpoons P + A$, the retinal concentration of the photosensitive material, S, at the moment of change-over from light to dark adaptation would be least in experiment 1 with the greater light adaptation.

Following the greater light adaptation, the concentration of photosensitive material, at first low, would rise when the subject was placed in the dark, until it was equal to the concentration existing in the retina at the moment of change-over in experiment 2. According to Hecht, the log of the threshold energy in the two cases should now be equal, because the concentrations of photosensitive material are alike. The only difference between the two experiments is that this equal threshold energy is reached at a later time in experiment 1.

From this point onward the rate of accumulation of the sensitive material should be the same in both experiments. Thus the shape of the log. threshold energy-time curves should also be the same and it should be possible to superimpose two curves following different degrees of light adaptation merely by shifting them parallel to the time axis.

This one cannot do in measurements obtained from human subjective experiments, because the curves are of different shape. Thus the simple scheme $S \rightleftharpoons P + A$ cannot be the whole truth.

The recovery of sensitivity is slower the longer the time of light adaptation, *i.e.*, the curves become more gentle in slope.

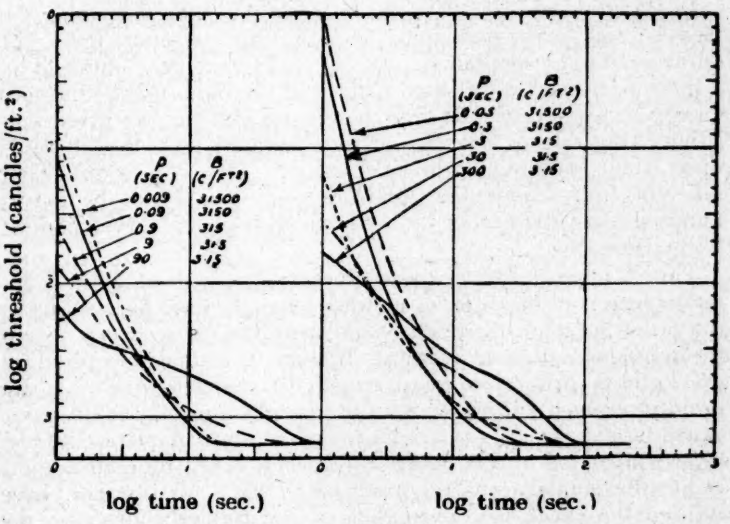


FIG. 2.—(After Crawford). Recovery curves of foveal sensitivity. The product of p, the light adaptation time, and b, the light adaptation brightness, is 283 for the left and 945 for the right diagram.

Crawford's very complete investigation (1946) illustrates this point (Fig. 2). For the results in this figure, the product of the light adaptation brightness and the time of its application was the same for all the curves in each diagram, so that the amount of light energy applied was similar for each member of the family of curves. To some extent the light adaptation time and brightness are interchangeable because the resulting dark adaptation curves are similar in shape, but if the time is prolonged for a matter of minutes (and the brightness appropriately reduced to maintain the quantity of light constant) a delay of recovery sets in which gives the curves the appearance of being crossed over each other. This " cross over " effect is only shown when the time of light adaptation is of several minutes' duration.

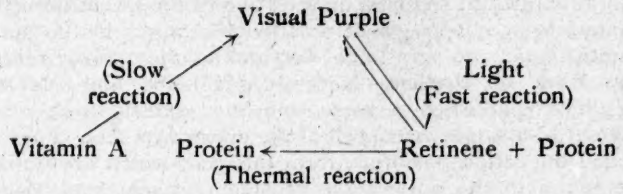
Wald's results also show the " cross over " of the curves, and Elsberg and Spotnitz (1938) have shown that increase of time is more effective than increase of brightness in delaying the recovery of the sensitivity of the fovea.

Haig (1941) could not demonstrate this effect, but when his results are compared with the more complete ones of Crawford (1946) it appears that his choice of the quantities for the time and brightness was unfortunate in that the particular values used do not demonstrate the effect.

In Wright's results (1946), the shape of the curve describing the recovery of foveal sensitivity to red light depends upon the duration of light adaptation. These results have been obtained by a binocular matching method instead of the more usual threshold energy measurement. Wright points out that for any given sensitivity, the rate of recovery at that point in the curve depends upon the preceding light adaptation. His curves following different light adaptation times certainly could not be superimposed upon each other by a simple shift of the curves parallel to the time axis.

Thus it appears that in those experiments where the light adaptation time is of the order of minutes, changes have been set up in the visual mechanism which result in a delay of recovery during the subsequent dark adaptation. It seems that time is required for the light to bring into play sensitivity changes which are not rapidly reversed and which are not brought into play to the same extent by increases in the brightness of the light adaptation source. The explanation of this delay in recovery, given by each author, is broadly similar. Wald and Clark (1937), for instance, have utilized the effect as confirmation of the former's views on the nature of the photochemical process.

According to Wald and Clark the events in the photochemical system may be represented thus :—



The breakdown of visual purple to retinene + protein is accomplished by light, and a further thermal conversion of retinene to vitamin A occurs. The visual purple may then be resynthesized either from retinene and protein or from vitamin A and protein, and the speed of the former reaction is postulated as greater than that of the latter.

Thus after a short exposure to a high brightness retinene would be the main photoproduct, there being little time to produce vitamin A. Recovery in the dark would then be rapid since it would rely on the fast reaction, retinene-visual purple. On the other hand, a longer exposure to a low brightness would allow vitamin A to be formed during light adaptation, so that the recovery would be more dependent on the vitamin A-visual purple process and therefore slower. A combination of these two processes could result, according to Wald, in a family of dark adaptation curves of differing slope.

Hecht, Haig, and Chase (1936) have followed Wald's explanation, and Wright (1946) has also come to the conclusion that regeneration of the sensitive substances may take place in two ways; one directly from photoproducts and the other, more slowly, from some reservoir of material the outflow from which is restricted. Crawford (1946) merely states that the effect could be explained by " . . . some sort of secondary reaction, or, possibly, diffusion of the end products of the initial reaction."

A different explanation has recently been given by Dartnall (1948). He postulates that the reduction of sensitivity in the light-adapted eye is due to the accumulation of large quantities of indicator yellow. Thus, after prolonged light adaptation, not only must the sensitive pigment visual purple be resynthesized, but also the indicator yellow must be destroyed, processes which would together lead to a long time of recovery. After short light adaptation times, only small amounts of indicator yellow have been formed. The recovery would then depend mainly on the fast resynthesis of the visual purple.

No author suggests, however, that variations in light adaptation

may have succeeded in separating to some extent the nervous and photochemical contributions to visual adaptation. The " cross-over " of Crawford's curves may be due to the initiation by long continued light adaptation of sensitivity changes in the nervous apparatus which are slow to develop and are only slowly reversed.

The Work of Hartline.—Recently, Hartline and McDonald (1947) have published a most complete investigation into the behaviour of a single visual cell of the eye of *Limulus*. They have recorded the action potentials from this cell, which are similar to those found in the optic nerve of other animals, and with this record have followed the dark adaptation of the cell after light adaptation for varying times to sources of various brightnesses. They found that for a considerable range of time and intensity, increases of either had a similar effect upon dark adaptation, but if the time of light adaptation was prolonged the " cross-over " effect noted above in the results from subjective experiments was observed. Hartline and McDonald follow Wald's explanation of this delay in recovery, but the effect may equally well be due to the appearance of a nervous component of visual adaptation. Hartline and McDonald's work would suggest that a nervous component in adaptation in man is confined to the visual receptors themselves. They might alter their sensitivity to the products of the photochemical reaction.

Indirect Adaptation.—Some of the strongest evidence in favour of a nervous component in adaptation is derived from experiments in which the adapting light is viewed indirectly. Using the binocular matching technique developed by Wright (1934), Schouten and Ornstein (1939) have studied the effect upon the foveal sensitivity of stimulation of a small area of the peripheral retina by a glare source of light. The left eye was used as a reference eye and was maintained in the dark-adapted state. The right, or test eye, could view a test stimulus with the fovea, together with the image of the glare source which did not fall on the fovea. A comparison between the test stimulus seen at the fovea of the eye stimulated by the glare and another stimulus seen with the fovea of the dark-adapted reference eye could be made by means of a binocular match.

With this apparatus Schouten and Ornstein found that there was a rapid reduction in foveal sensitivity of the test eye when the glare source was applied; a reduction which was complete in 0·1 sec., and they refer to this effect as α-adaptation.

If the glare source was extinguished within a few seconds, the foveal sensitivity made a rapid, but not immediate, recovery. If light adaptation was continued for a few minutes, however, recovery was much slower and several minutes would elapse before

it was complete. This the authors call β-adaptation and point out that this adaptation has no noticeable effect upon the foveal sensitivity during the period of light adaptation. It is only observed as a delay in recovery during the subsequent dark adaptation.

Since the glare-source stimulus is not applied to the fovea, and since there is a rapid depression of sensitivity in that region, Hecht's simple photochemical explanation of adaptation is quite inadequate, and Schouten and Ornstein have considered two main alternatives. First, that the adaptation is due to scattered light illuminating the fovea and causing light adaptation in the ordinary way, and second, that some " electrical effect " is set up in the retina by the image of the glare source and that the foveal sensitivity is depressed by such an effect being transmitted over the retina.

From the results of an experiment employing trans-scleral illumination, they come to the conclusion that α-adaptation is an " electrical " phenomena not due to the effect on the fovea of the scattered light in the globe of the eye. Their precise idea as to the nature of the " electrical " effect is a little difficult to discover from their paper. They also believe that β-adaptation, which more closely resembles the recovery of sensitivity as measured in threshold experiments, is due to " . . . the electrical processes in the retina."

Wright (1946) has repeated some of Schouten and Ornstein's experiments and confirms their results. He, too, thinks that scattered light is unlikely to have played a major part in the effect and follows Schouten and Ornstein in considering that the α-process is due to " . . . the electrical inhibitory action . . . " of the large response from the retina stimulated by the glare source upon the response from the foveal retina stimulated by the much less intense test light. Wright prefers to explain the β-process at the fovea by postulating that there is in that region a diminution of the concentration of photo-sensitive material by a process of " photochemical drainage " towards the region of the retina stimulated by the glare source.

Crawford (1937) also measured the recovery of sensitivity in the retina after adaptation to a glare source and reported his results prior to those given by Schouten and Ornstein (1939). In his experiment the dark adaptation of both the fovea and parafovea (14° from the fixation point) were followed by threshold energy measurements following light adaptation either to a glare source situated 2·9° above the fovea or to a uniform background brightness, the image of which included and surrounded the fovea. This latter experiment was similar in every way to the usual measurements of dark adaptation. The two light adaptation sources were

equivalent, in that for each source the same amount of energy had to be applied to the test area during light adaptation to elicit a threshold response.

From Crawford's results it is clear that light adaptation produced by the glare source is similar in every way to that from the uniform background brightness so far as the subsequent dark adaptation is concerned.

Thus, in the indirect adaptation experiments, an effect has been achieved at the fovea by the image of a glare-source not at the fovea, and it is difficult to see how a simple photochemical theory such as Hecht's could explain this effect, unless one postulates that scattered light is the cause of the foveal sensitivity change. Since this is unlikely a " photochemical " theory must explain how it is that alterations in the concentrations of the foveal photosensitive materials can be produced by stimulating another portion of the retina.

Wright's " photochemical drainage " explanation of the β-adaptation process requires an actual movement of sensitive material in the retina. It is generally held, however, that the pigment visual purple is intimately associated with the structure of the rod cells (Schmidt, 1938). If this is so, visual purple is unlikely to move about in the retina as suggested by Wright, and although it is possible that the β-process has a photochemical explanation, there is no real evidence for Wright's idea.

From Crawford's experiment (1937) it seems that a glare source may delay recovery of sensitivity for a time equal to that found in experiments in which a uniform light adaptation source is used, and it may well be that the usual threshold measurements follow the recovery of a β-adaptation process.

In view of the difficulties of explaining them by a " photochemical " theory, the results from indirect adaptation experiments point to the existence in the visual mechanism of components to adaptation other than photochemical ones. Such processes may well be nervous in origin.

The Effect of Light Adaptation of One Eye upon the Sensitivity of the Other. — In Hecht's photochemical theory of visual adaptation the nervous system behaves merely as a signalling apparatus so that the photochemical events may be relayed to the brain. Thus if it could be shown that light adaptation of one eye had an appreciable effect upon the light sensitivity of the other, it would suggest strongly that there was, in addition to change in concentration of photochemical substances, some change in the sensitivity of the nervous system, because it is difficult to see how stimulation of the nerves of one eye could cause alterations in the concentrations of the photosensitive materials in the other.

Unfortunately, opinion as to the experimental facts is not unanimous. Of the authors mentioned by Dorothy Adams (1929) some regard the two eyes as independent, whereas others ascribe to light adaptation of one eye various effects upon the sensitivity of the other. Helmholtz (1924) held that the two eyes are independent. Of later workers, Crawford (1940) could find no change in the value of the threshold energy of a fully dark-adapted eye, when the light adaptation of its fellow was changed.

Mandelbaum (1941) has also measured the dark adaptation in one eye whilst applying a bright light to its fellow. No difference could be detected between one curve obtained in the normal way after light adaptation and another during which the opposite eye was subjected to a brightness of 6000 ml. through a 2 mm. pupil for several periods during the measurements.

Wright (1934) has devised a method for studying the adaptation of the eye, which relies upon a large measure of independence between the two eyes. In his method one eye is maintaind in the dark-adapted state and is used as a reference eye. The other is brought to various levels of adaptation and its response to various stimuli compared with that of the reference eye by a binocular match between two fields, one of which is seen with each eye. The method assumes that light adaptation of the test eye has only a very small effect upon the dark-adapted reference eye. Wright (1946) says of his method, " The validity of the binocular method depends on the assumption that the sensitivity of the left eye is constant throughout the experiment and can, therefore, be used as a reference standard against which changes in the right eye can be recorded. This assumption is not strictly correct, since adaptation of the right eye undoubtedly induces minor changes in the left. At the same time tests by the threshold method . . . show quite definitely that any effect which is produced on the left eye is of a second order magnitude, and in no sense comparable to the much greater changes produced in the right eye. Such effects can, therefore, be neglected."

Schouten and Ornstein (1939) and Craik (1939) have also used Wright's binocular method for the study of adaptation, and have made similar assumptions concerning binocular interactions.

On the other hand, Elsberg and Spotnitz (1938) have marshalled evidence to show that adaptation of one eye does affect the sensitivity of the other and in their own experiments their results cannot be said to show only " minor changes " in the second eye. Dunlap (1921) also finds sensitivity changes in one eye due to stimulation of its fellow.

Helmholtz (1924) reminds us, however, that it is not easy to bandage one eye so that all light is excluded, and Crawford (1940)

suggests that in experimental systems which do not employ Maxwellian view, some leakage from the light adaptation system may occur to the dark-adapted eye and that this might account for any sensitivity changes found.

It is true that those authors who find central adaptation effects are those who do not use Maxwellian view and such a simple explanation may be correct.

Thus, unfortunately for those who hold that adaptation has a central nervous component, the balance of evidence is in favour of the independence of the two eyes. This would suggest that the site of the adaptation process, whether nervous or photochemical, is within the eye itself.

Craik and Vernon's Blinding Experiment. — Further support for the peripheral nature of visual adaptation was obtained by Craik and Vernon (1941). These authors were able to produce temporary blindness in an eye by applying pressure to the sclera. Then with a dark-adapted eye in a blinded state, light adaptation for a 3-minute period to a brightness of 12,000 e.f.c. through a 2 mm. pupil was undertaken. At the end of the light adaptation the eye was allowed to recover rapidly from the effect of the pressure and the subsequent dark adaptation curve was measured. This curve was found to be no different from a curve obtained after similar light adaptation of a normally functioning eye, if a slight delay in the initial stages of dark adaptation due to the recovery from the pressure may be neglected. The authors conclude, "The normality of the dark adaptation curve obtained with an eye which has been blinded during the bright adaptation period shows that light adaptation, both of rods and of cones, is a retinal reduction of sensitivity and not a cortical one, since the primary stimulation never reached the higher centres."

Some Fallacies.—Protagonists of a nervous theory of adaptation are apt to include certain evidence which is not valid. Visual adaptation is a change in light sensitivity, which is initiated by the presence or absence of a light stimulus. Before an effect can be considered as part of the normal visual adaptation mechanism it must be shown firstly, that light is the stimulus which causes the reaction, and secondly, that a change in the sensitivity to light is involved.

It is possible for light to have effects upon the nervous system, such as the alteration of electrical rhythms in the cerebrum, which, because a change in light sensitivity is not involved, cannot be part of the adaptation process. Again, light may alter the sensitivity of the visual mechanism to electrical stimulation (Bouman, 1935), but here too the effect cannot be called visual adaptation.

Sensitivity changes may occur in response to stimuli other than

light, such as sound (Kravkov, 1934), and stimuli applied to the autonomic system (Kekcheev, 1942), but here again these effects do not support a nervous theory of visual adaptation even though their site of action is clearly within the central nervous system, because no alteration in the light sensitivity of the mechanism is involved.

The Work of Granit.—If visual adaptation be entirely a photochemical phenomenon, it should be possible, in animals, to

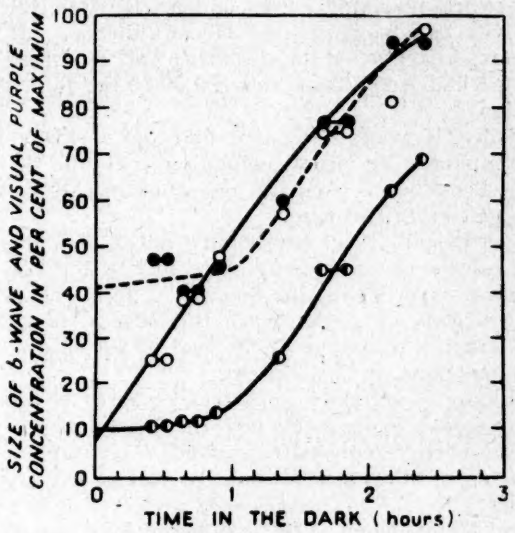


FIG 3. (After Granit and others).—A comparison between the recovery of the b-wave of the frog's electroretinogram and the accumulation of visual purple during dark adaptation.

◐ Recovery of sensitivity to test light of low intensity. ● Recovery to light of higher brightness. O Visual purple accumulation.

measure the increase in concentration of visual purple during dark adaptation and to record the sensitivity of the eye to light under similar conditions. If Hecht's views are correct, the sensitivity increase should run parallel to the increase in the visual purple concentration. Granit, Munsterhjelm, and Zewi (1939) have performed such an experiment on frogs and some of their results are shown in Fig. 3.

Here the progress of the sensitivity increase is followed by measuring the size of the b-wave of the electroretinogram, which

wave is considered to be the part of the trace most closely associated with the discharge in the optic nerve. The visual purple concentrations, which are determined by killing the animals at suitable moments during dark adaptation and extracting the pigment from the retina, are expressed as a percentage of the maximum concentration achieved in the dark. Granit points out that the mechanism did not recover at once from the depression of sensitivity created by light adaptation, whereas regeneration of visual purple began as soon as the animal was transferred to the dark. There was clearly no simple correspondence between concentration and sensitivity as is suggested by Hecht's theory. It appeared from these experiments that the sensitivity only recovered when the visual purple had accumulated to some 50-60 per cent. of its dark concentration.

Superficially, it would seem that here too a slowly reversible nervous component to visual adaptation could be delaying the recovery of sensitivity. Actually one must beware of accepting such a suggestion in this case.

Firstly, as Peskin (1942) has pointed out, Granit has used the size of the b-wave as the measure of sensitivity and not, as is the case in human experiments, the quantity of light energy required to produce a constant response (in this case a constant size of b-wave). Granit's technique might lead to a measured delay in recovery where none, in fact, existed.

This criticism is certainly important because, as may be seen from Granit's other experiments with the microelectrode technique in which the energy required to produce a constant response in frog's optic nerve fibres is measured, recovery of sensitivity begins much earlier.

Secondly, Mandelbaum (1941) has maintained that Granit and others (1939) failed to take proper precautions against visual purple regeneration. Peskin (1942) claims to have shown that visual purple regeneration in the living frog's eye is delayed for 10 minutes or so when bright sources are used for light adaptation. If these points are valid, it may be that the non-correlation is in some way incorrect.

On the other hand, another experiment (Granit, Holmberg, and Zewi, 1938) supports the failure to obtain a simple correlation. By applying to living frog's eyes small quantities of monochromatic light, these authors found that the b-wave could be completely suppressed, *i.e.* the sensitivity of the visual mechanism greatly reduced, without there being any detectable diminution in the amount of visual purple that could be extracted from the retina after similar monochromatic illumination. That this is due to failure to destroy the visual purple with monochromatic light, and

not to regeneration during extraction, is shown by the observation that the same amount of monochromatic light would only produce a diminution of about 2 per cent. in the concentration of a visual purple solution. In such a solution regeneration of 98 per cent, of the visual purple would be most unlikely.

Thus there is evidence here also which does not fit easily into a photochemical explanation of adaptation.

A Pupillary Experiment.—Recently the author (Thomson, 1949) has performed some experiments which strengthen the belief that there is a nervous component to adaptation.

Two series of dark adaptation measurements were made following a standard 15-minute period of light adaptation. The pre-light adaptation treatment in the first series was a period during which the eyes were in darkness, and in the second, in a bright outdoor light. A difference was detectable in measurements of pupillary diameter made during the subsequent dark adaptation, larger diameters being found after the period in darkness.

After considering several possibilities, it appeared improbable that the photochemical system could influence the nervous mechanism when the eyes were in the dark. Thus the pupillary differences found were most likely maintained by nervous messages other than those initiated by a light sensitive substance, for example, the discharges found by Granit (1947) in dark-adapted and unstimulated single fibre preparations.

These discharges could signal to the pupillary muscles whilst the eyes are in the dark sensitivity differences produced in the nervous mechanism by the pre-light adaptation treatment.

Summary

The idea presented in this article is that the sensory receptor cells in the retina, which are in contact with the photochemical system of the eye, play a part in visual adaptation. It is proposed that these cells alter their sensitivity to the end-products of the photochemical reactions and that this sensitivity change is in addition to any which may be attributed to the photochemical mechanism.

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STREPTOMYCIN AND PROMANIDE IN EXPERIMENTAL OCULAR TUBERCULOSIS*

BY

J. MACASKILL *and* M. WEATHERALL

Edinburgh

IT is known that bacteriostatic concentrations of streptomycin can be produced in various tissues of the rabbit's eye after systemic administration (Leopold and Nichols, 1946) ; after application to the conjunctival sac when the cornea is inflamed or abraded, but not otherwise (*Id, ibid.*, and Bellows, Burkholder, and Farmer, 1947); after intravitreous injection; and, rather transiently, after subconjunctival administration (Gardiner, Michaelson, Rees, and Robson, 1948). There appear to be no measurements of the penetration of sulphones into the eye, but Steenken, Wolinsky, and Heise (1946) obtained therapeutic results in guinea pigs with experimentally induced tuberculosis of the eye by subconjunctival or oral administration of sodium p-p'-diaminodiphenylsulphone-N-N'-didextrose sulphonate (" Promin " or " Promanide "). The present paper records some observations on the efficacy of streptomycin and Promanide under various conditions in experimentally produced tuberculosis of the iris and ciliary body of the rabbit's eye.

Methods

In order to study the effect of supposedly therapeutic agents, it was necessary to produce a suitable experimental lesion, at least moderately consistently. Such lesions have frequently been produced in rabbits by inoculation of tuberculous material into the eyes (for early references, see Robson, 1944) and rather less reliably by systemic inoculation (Angevine and Huntington, 1941; Bablet and van Deinse, 1943). The number of organisms necessary to produce lesions apparently varies widely and depends on the strain of organism and the precise site of inoculation. In their very thorough study, Woods, Burky, and Friedenwald (1938) obtained irregular results with the standard strain H37, and produced a more consistent lesion by intra-aqueous inoculation of a strain obtained from human sputum, grown on hormone-bouillon containing 5 per cent. glycerine for four to eight weeks, and introduced as a filtered saline suspension, of which a single inoculum apparently contained about 10^5 organisms. Gray (1937)

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used if anything larger numbers of organisms, but infected the posterior chamber. Robson (1944) produced lesions by intracorneal injection of far smaller number of organisms, about 100 human or as few as about 5 of a bovine strain. His data indicate that a hundred-fold increase in the number of organisms increases only slightly the rate of onset and severity of the lesions. For the present purpose, intra-aqueous inoculation seemed to us most likely to produce lesions approximating to those observable clinically, and after some preliminary experiments, with various strains obtained from human lesions, good lesions were obtained with a dose of about 10^4 organisms of a moderately virulent strain. We failed to produce lesions with inocula containing less than 10^3 organisms of any strain. Larger inocula or more virulent strains rapidly produced severe lesions. There was considerable variation in sensitivity to different strains, as is described below.

Strains of *Mycobacterium tuberculosis*, human type, were isolated from the sputum of consumptive patients and cultured on Loewenstein-Jensen egg medium. Colonies from two to three week old subcultures (at 37°C.) were picked into sterile 0·9 per cent. sodium chloride and ground in a sterile mortar, and the suspensions were matched against standard opacity tubes so that the number of bacilli in 1 ml. might be estimated approximately. Suitable dilutions for inoculation were prepared from these suspensions. As it was difficult to prepare a uniform suspension of bacilli and as it seemed likely that some variation in the lesions produced was due to the injection of aggregates containing variable numbers of organisms, the expedient was tried in one experiment of picking the colonies into sterile saline containing 0·02 per cent. sodium dodecyl sulphate. This concentration of detergent was about the highest expected to be harmless to the organisms during the short period for which they were exposed to it (*cf.* Baker, Harrison, and Miller, 1941) and the final concentration injected into the eyes (0·0002 per cent.) was well below levels found to be injurious with other anionic detergents applied to abraded corneae (Leopold, 1945).

Adult rabbits of both sexes were used. Inoculation was made into the anterior chamber in front of the limbus, under thiopentone anaesthesia (25 mg./kg. body weight). The severity of the lesions produced was assessed by clinical examination of the eyes during life, by post mortem search for dissemination of the infection, and by histological examination. Tuberculin tests were performed, but the responses were weak and erratic, and have been of no value. Streptomycin (Merck) was used by subconjunctival or intravenous injection, and Promanide (Parke Davis) by intravenous injection.

Experiments

Two sets of experiments have been performed. In the first, four dilutions of four different strains of tubercle bacilli were introduced into the sixteen eyes of eight rabbits. In these rabbits an endeavour was made to introduce a fixed amount of the suspension of tubercle bacilli into the anterior chamber. However, on withdrawal of the needle a variable amount of fluid leaked away, and as it was doubtful whether this fluid was aqueous humour or inoculum or a mixture of both, the accuracy of the dose was uncertain. Four of these rabbits were treated with streptomycin subconjunctivally, as described below; and, as severe lesions were

produced rapidly, this experiment was terminated after three weeks. In the second set of experiments a suspension of tubercle bacilli of uniform concentration was used. With approximately 0·1 ml. of the suspension in a syringe, the contents of the syringe and the aqueous were well mixed by depressing and withdrawing the piston of the syringe several times while the needle was in the anterior chamber, and the syringe was finally removed containing 0·1 ml. of the mixed fluid, so that the final volume of fluid in the anterior chamber was not increased. Less leakage occurred than in the first set of experiments. Sixteen rabbits were used: the right eyes were all inoculated with a suspension containing 0·002 per cent. sodium dodecyl sulphate and the left eyes with a suspension which contained no detergent. When iritis was present in nearly all the rabbits, they were divided into four groups according to the severity of their lesions, and were treated, as described in the section on results, for one week. After treatment they were sacrificed at various times up to forty-five days for post-mortem and histological examination. The severity of the lesions was assessed for about six weeks from the time of inoculation mainly by the extent and degree of inflammation of the iris. Mild, moderate and severe lesions were scored one, two and three respectively, and intermediate scores were used in ambiguous cases. Later, the extent of caseation was assessed and scored similarly. The observer was at all times unaware of the previous score and of the treatment which the rabbit had received, and was occasionally shown the same rabbit twice in the same series of observations: in such circumstances the scores usually agreed exactly and rarely differed by more than one half unit.

The second set of experiments was factorially designed, and the arbitrary scores were analysed on lines described by Ficher (1942). Results were deemed significant when the estimated probability of their occurring by chance was less than one in a hundred, and insignificant when they might have occurred more often than once in ten times. Intermediate probabilities were not in fact met.

Results

The first experiment (Table I) was designed partly in order to find an optimal dose and strain of tubercle bacilli for the present purpose, and the wide variation in the lesions was expected. There were substantial differences in the progress both of lesions produced by the same strain at different dilutions and of lesions produced by different strains at the same dilution. However, the relative rates of progress of untreated lesions were reasonably constant, and sufficiently so to allow therapeutic trial in a proportion

TABLE I

The severity of ocular lesions in rabbits of the first series of experiments.

Days from inoculation		7	12	17	21	Treated on days	Remarks
Rabbit 48, strain 3798,	10^4 orgs./ml. ...	0	0	$\frac{1}{2}$	$\frac{1}{2}$	13-17	—
	10^6 orgs./ml. ...	$\frac{1}{2}$	$\frac{1}{2}$	$1\frac{1}{2}$	2		
Rabbit 49, strain 3798,	10^7 orgs./ml. ...	$\frac{1}{2}$	1	$1\frac{1}{2}$	—	None	Died on 19th day
	10^8 orgs./ml ...	2	2	$2\frac{1}{2}$			
Rabbit 326, strain 3253,	10^4 orgs./ml. ...	0	0	$\frac{1}{2}$	1	None	—
	10^6 orgs./ml. ...	0	1	1	1		
Rabbit 335, strain 3253,	10^7 orgs./ml. ...	0	$1\frac{1}{2}$	$1\frac{1}{2}$	2	7-17	—
	10^8 orgs./ml. ...	0	2	2	$2\frac{1}{2}$		
Rabbit 340, strain 3800,	10^4 orgs./ml. ...	0	0	$\frac{1}{2}$	1	None	—
	10^6 orgs./ml. ...	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$		
Rabbit 341, strain 3800,	10^7 orgs./ml ...	$2\frac{1}{2}$	2	—	—	7-12	Killed on 12th day
	10^8 orgs./ml. ...	3	3				
Rabbit 343, strain 3808,	10^4 orgs./ml. ...	$\frac{1}{2}$	$\frac{1}{2}$	2	$2\frac{1}{2}$	13-17	—
	10^6 orgs./ml. ...	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$		
Rabbit 344, strain 3808,	10^7 orgs./ml. ...	$2\frac{1}{2}$	2	$2\frac{1}{2}$	—	None	Killed on 18th day
	10^8 orgs./ml. ...	$2\frac{1}{2}$	$2\frac{1}{2}$	3			
Mean score, untreated, 10^4 and 10^6 orgs./ml.		$\frac{1}{4}$	$\frac{5}{8}$	1	$1\frac{3}{8}$	None	—
Mean score, treated, 10^4 and 10^6 orgs./ml.		$\frac{1}{4}$	$\frac{5}{8}$	$1\frac{1}{4}$	$1\frac{5}{8}$	13-17	—
Mean score, untreated, 10^7 and 10^8 orgs./ml.		$1\frac{1}{4}$	$1\frac{7}{8}$	$2\frac{3}{8}$	—	None	—
Mean score, treated, 10^7 and 10^8 orgs./ml.		$1\frac{1}{2}$	$2\frac{1}{8}$	—	—	7-12 or 17	—

The underlined scores are those for eyes during or after treatment with streptomycin (30 mg. to each eye subconjunctivally daily).

of the animals while the rest served as controls. Two of the four rabbits which had received large inocula were treated from the seventh day onwards, and two of the four which had received small inocula were treated from the twelfth day. The second pair were those which had been inoculated with the same strains as the control pair of the large inocula. The treatment consisted of the subconjunctival injection of streptomycin (30 mg. in 0·3 ml. sterile 0·9 per cent. sodium chloride solution to each eye) once daily, and was continued until the seventeenth day from inoculation unless the animal died sooner. The control rabbits were injected similarly with 0·9 per cent. sodium chloride solution.

The rabbits which had large inocula developed very severe lesions. Two of them were sacrificed when they had developed panophthalmitis, and one died. Except in the mildest cases, all these animals showed an acute inflammatory reaction in the iris and ciliary region in a few days. The reaction was accompanied by a mild conjunctivitis with a thin purulent discharge, and at

first had no typically tuberculous features. Between the second and third week small patches of caseation developed. The milder cases showed less or no initial inflammation, and sometimes slight oedema of the iris and irregularity of the pupil were the only signs which preceded the appearance of areas of caseation. This experiment was terminated after three weeks because of the number of animals which had died and because of the severity of the lesions in the survivors.

No benefit whatever was observed either clinically or on subsequent hisological examination of these eyes from subconjunctival streptomycin treatment, and the rate of progress of all the lesions was apparently unaffected.

In the second experiment, in which a standard dose of tubercle bacilli was used in all the rabbits, the lesions were much milder and slower in onset. Mild inflammatory reactions developed in the irides between the seventeenth and twenty-seventh days, and the first signs of caseation a few days later. In untreated animals the iritis was maximal about the thirty-fifth day, and then quiesced, while the centres of caseation extended and coalesced to form areas of various size, sometimes involving much of the anterior chamber, or invading the cornea and other surrounding structures. Twenty-eight days after inoculation the rabbits were divided into four

TABLE II

The severity of lesions in rabbits of the second series of experiments.

	Severity of iritis (arbitrary scale) Mean ± Standard Error			Severity of caseation (arbitrary scale) Mean ± Standard Error		Lesions in animals killed		
						Lungs		Other Organs
Days from inoculation	28	37	52	56	72	56	72	72
Number of rabbits in group	4	4	3	3	2	1	1 or 2	1 or 2
Group O ...	0.56±0.17	0.86±0.20	0.79±0.26	2.17±0.38	2.00	+ +	+	0
Group P ...	0.42±0.11	0.61±0.16	0.75±0.26	1.53±0.33	1.38	+ + +	+ + +	Liver (2) Kidney (1)
Group S ...	0.58±0.23	0.48±0.23	0.36±0.42	0.79±0.47	0.12	0	0	0
Group PS	0.37±0.12	0.42±0.16	0.21±0.15	0.50±0.17	0.31	0	0	0

One animal in each of these groups died before the date indicated. The figures given are calculated from the latest available scores for the rabbits concerned. As the lesions in these rabbits were if anything progressing, the scores tend to be underestimated. The animals were treated with promanide or streptomycin on the 28th to the 34th days from inoculation.

groups of four, according to the severity of the lesions, and in each group the four rabbits were allotted to different treatments by a random procedure. The treatments consisted of :—

Group O—No treatment.

Group P—Promanide, 150 mg./kg. intravenously at twelve-hour intervals.

Group S—Streptomycin, 30 mg./kg., intravenously, at twelve-hour intervals.

Group PS—Promanide and Streptomycin as above.

Treatment was continued for seven days. The rabbits which had been grouped as most severe before treatment were sacrificed two days after the end of treatment, the next group twenty-eight days

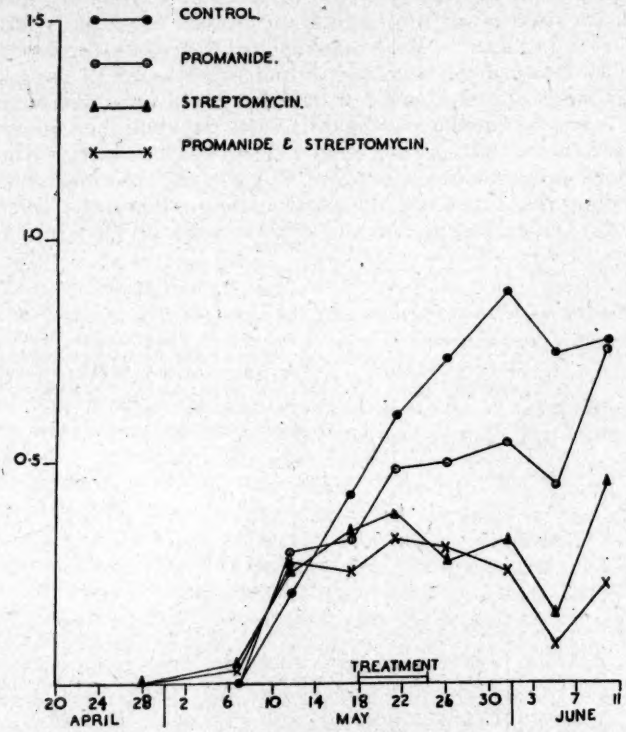

FIG. 1.—The progress of the iritis in rabbits of the second series of experiments. The points represent the mean severity of the iritis assessed on an arbitrary scale, in groups of four rabbits which were inoculated with tubercle bacilli in the aqueous humour on April 20 and were treated with promanide and streptomycin as indicated from May 18 to 24.

FIG. 2.—Eye of streptomycin + promanide treated rabbit 44 days after end of treatment.

FIG. 3.—Eye of control rabbit 44 days after end of treatment.

and the survivors forty-five days after the end of treatment for post-mortem and histological examination. The results are shown in Table II and Figs. 1, 2, and 3, and require little comment. All the treated groups did better than the controls, but the improvement was significant only in the streptomycin groups. The difference was equally observable in the milder iritis and lesser caseation, both macroscopically and histologically (Figs. 4-7), and

FIG. 4.—Group O. No treatment.

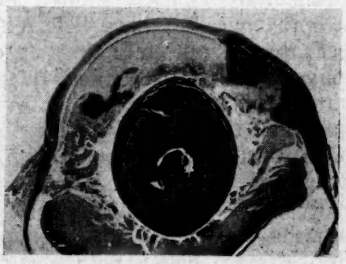

FIG. 5.—Group P. Promanide only.

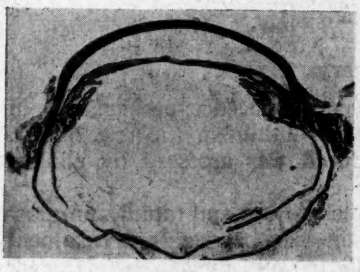

FIG. 6.—Group S. Streptomycin only.

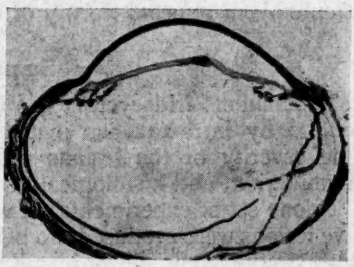

FIG. 7.—Group PS. Promanide and Streptomycin.

FIGS. 4–7.—Comparison of extent of caseation in cases of average severity from each of the four groups.

in the diminished spread of the infection to other organs. The difference between the Promanide-Streptomycin group and the Streptomycin alone group was quite insignificant, and no difference was observed between the behaviour of the eyes which had been inoculated with the suspension containing detergent and those not so inoculated.

Discussion

Therapeutic results have been obtained with streptomycin under suitable conditions, but not more than mitigation of lesions has occurred: in none of our rabbits was a definitely established tuberculous infection of the eye eradicated. Our results appear somewhat more favourable than those of Grignolo (1948) in guinea-pigs: he obtained benefit from streptomycin only when it was given before lesions had developed, but he was probably dealing with a heavier infection than was used in our second series. The present data are inadequate as a basis for comparison of the efficacy of different routes of administration, as the lesions were not comparable in the two series. The beneficial effect, if any, of Promanide is clearly limited and no appreciable synergism with streptomycin has been detected. The schedules of dosage were perhaps not optimal: they were designed to make the most prolonged use of a limited quantity of material, and extensive alternatives are possible. In Woods' extensive experimental work on ocular tuberculosis he investigated the efficacy of streptomycin used systemically, on animals rendered immune-allergic by previous systemic tuberculous infection. Using slightly bigger daily dosage than ourselves and for a period of treatment of $2\frac{1}{2}$ months, he found that groups treated by streptomycin were dramatically better than the control group. As none but the mildest forms of tuberculous disease of the uvea in man are amenable to present forms of treatment the systemic use of streptomycin appears worthy of trial.

Summary

Tuberculous iridocyclitis has been produced experimentally in rabbits by intra-aqueous inoculation of human tubercle bacilli. The severity of the lesions produced was assessed by clinical examination, and histologically.

In one set of experiments, in which severe and rapidly progressive lesions were produced, no benefit was observed from treatment with streptomycin subconjunctivally (30 mg. to each eye daily for five or ten days).

In a second set, in which milder lesions developed, streptomycin

intravenously (30 mg./kg. twice daily for seven days) substantially ameliorated the lesions but did not completely eradicate infection in any case.

Promanide intravenously (150 mg./kg. twice daily for seven days) either alone or in conjunction with streptomycin, appeared to be slightly beneficial, but the results were quite insignificant.

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THE ACTION OF ESERINE UPON THE EYE FOLLOWING THE USE OF ATROPINE*

BY

C. R. S. JACKSON

Nuffield Laboratory of Ophthalmology, Oxford

IN view of the conflicting reports in ophthalmological literature about the action of eserine on an eye previously under the influence of atropine, it seemed desirable to re-examine the problem.

Pharmacological writers are in no doubt of the mode of action of these drugs and no long discussion is proposed here. The acetyl-choline produced at the parasympathetic nerve-endings is normally removed almost as rapidly as it is formed by the action of the enzyme cholinesterase which is universally present in the tissues. Eserine has no direct action on nerve-endings but acts solely as an anti-cholinesterase, thus allowing the concentration of acetyl-choline to rise and so augmenting the response of the tissue to the activity of its nerve. This hypothesis depends mainly upon the fact that smooth muscle such as that in the iris, which is innervated by a cholinergic nerve, is unresponsive to eserine if the nerve is cut and time allowed for it to degenerate. Under these circumstances no acetyl-choline is produced by the degenerate nerve-endings and therefore the anti-cholinesterase activity of eserine can evoke no response. Here is the distinction between eserine and pilocarpine, since the latter acts directly on the muscle of the iris.

Atropine paralyses the muscle of the iris to oculo-motor impulses, or rather it reduces the sensitivity of the muscular fibres to the presence of acetyl-choline, so that dilation of the pupil results from the tonic pull of the dilator fibres. The question is whether or not the " paralysis " produced by atropine is absolute. Ophthalmological writers during the past few years almost all say that the paralysis is absolute, and many of them state specifically that " the mydriasis of atropine is irreversible " (Duke-Elder, 1932, 1934; Parsons and Duke-Elder, 1948; Traquair, 1948; Walsh, 1947; Douthwaite, 1949; Doggart, 1949).

Before reviewing some early ophthalmological writings it is as well to see what the pharmacologists have to say about this.

Goodman and Gilman (1941) say that " . . . physostigmine and pilocarpine are capable of contracting the atropinized pupil . . . " and there are a number of references to experimental work bearing this out. Anderson (1905), who carried out some of the work on the denervated iris which has been mentioned above and mentions the work of Schultz (1898) in the same connection, says

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that physostigmine abolishes the mydriasis of atropine and mentions incidentally that pilocarpine will not do so. The question is also discussed by Henderson and Roepke (1937) who come to the same conclusion.

Sollman (1948) in his text-book of pharmacology agrees with this view and says . . . " The atropine effects (on the pupil) may be removed by drugs which stimulate the oculomotor receptors (pilocarpine, physostigmine, choline esters, muscarine) and *vice versa*." He also records a suggestion by Gifford in 1916 that eserine should be used after atropine until the pupil and accommodation have returned to normal.

Guyton (1940) in a review of the action of these and similar drugs, in speaking of their antagonisms, says that the effect of two drugs of opposed actions may be expected to be governed on a quantitative basis and not on any special antagonistic properties that the drugs might be thought to have on one another. Earlier in the same paper, however, he says . . . " Atropine prevents the action of choline compounds on structures innervated by cholinergic nerves."

To my mind, however, the most interesting papers are now of some antiquity and they derive increased interest from the fact that one is by Argyll Robertson.

Thomas R. Fraser (1863) first described the action of eserine on the eye and it was he, incidentally, who suggested the name we all use, after esere, as the ritual poison was named in Calabar (Rodin, 1947). Fraser's paper is very interesting and the following quotation is particularly pertinent " . . . (physostigmine can be used) . . . in mydriasis, whether dependent on the overaction of belladonna, or as a symptom of amaurosis, especially the hydrocephalic variety . . . as well as in many other cases which will suggest themselves to the ophthalmologist, this agent deserves a trial."

In the same year Argyll Robertson (1863) followed with a description of a series of experiments upon his own eyes. He showed first (experiment 2) that atropine dilated the pupil after eserine and that this dilatation could be reversed by eserine, and then (experiment 3) that eserine would contract in less than an hour the pupil which had previously been placed thoroughly under the influence of atropine. He concludes " . . . it is applicable in all instances when atropine is used to render the examination of the eye more perfect or simple."

If we can say that there is no special pharmacological basis for the antagonism between atropine and eserine, and can agree with Guyton (1940) that the problem is a quantitative one, it is reasonable to think that eserine would contract the pupil of the atropinized eye. Even in what we call " full atropinization " it

is likely that the concentration of atropine within the eye is not high and we know that smooth muscle is extremely sensitive to acetyl-choline in the presence of eserine. For example, leech muscle contracts in the presence of eserine when exposed to as low a concentration of acetyl-choline as two microgrammes per litre, or 1 : 500 million. If, therefore, the concentration of acetyl-choline in the eye is raised, as it is by the action of eserine, then the probability is that the iris sphincter will contract despite the previous application of atropine.

I have carried out a short series of experiments to re-investigate the problem.

Results

I. *Rabbits*

The first tests were made on rabbits. Guttae atropinae 1 per cent. were applied twice daily for ten days to both eyes of two rabbits. On the tenth day intensive application of eserine (one drop of 1 per cent. every minute) was started to the right eye of each animal. From full mydriasis at the beginning, the size of the pupils was reduced to one millimetre or less in fourteen minutes. The eserine was then stopped as one of the animals showed signs of eserine poisoning. Despite intravenous atropine given at once the animal died in a few minutes with muscular twitchings and increasing respiratory difficulty due to bronchial hypersecretion. It is unlikely that the animal absorbed the whole of the drug which was placed on the conjunctiva, as there was considerable lacrimation. If it did absorb it all, the lethal dose of eserine will have been about 9 mg.

In the other animal the eserine-treated pupil remained less than three mm. dilated for twelve hours, then it dilated slowly until it was the same size as its fellow in forty-eight hours. Both pupils were normal in six days.

II. *Humans*

(*a*).—A child of seven years old who had been under treatment with Ung. Atropinae 1 per cent. twice daily for five days and in whom there was full mydriasis had one drop at a time of 1 per cent. eserine put into the eye at intervals, as shown in the table below, and the size of the pupil was recorded. Retinoscopy was also carried out at intervals and the retinoscopy findings are shown. The return of ciliary muscle activity is very striking.

TABLE

Time (min.) ...	2	4	6	8	13	18	23	28
Pupil (mm.) ...	10	—	—	—	10	5	4	2
Retinoscopy ...	+5·5	—	—	—	+5·5	+3·75	+0·50	+0·50

After eight applications of eserine the drug was stopped. There was full miosis at forty minutes, slight dilatation was occurring at two hours, and the pupil was half-dilated, but active, five hours later.

(*b*).—The next patient was a youth of fifteen who had been using Guttae atropinae 1 per cent. twice daily for six days up to the time of the trial of eserine. There was full mydriasis at the start. He was given 1 per cent. eserine every minute for five minutes, and then every five minutes for a further half hour. At the end of that time the pupil was half-contracted and there was ciliary spasm to the extent of −3·0 D.S., his refraction having been emmetropic. Two days later, having had no treatment in the interval, he was comfortable and the near-point of the affected eye was 10 cm. as measured on the Livingston gauge, which would not have been the case had the effect of the atropine been allowed to wear off in its own time.

(*c*).—A man of thirty-one who had been treated with atropine 1 per cent. three times daily for seven days because of a contusion injury to the globe, was given four drops of 1 per cent. eserine at half-hourly intervals. His pupil size was 8 mm. at the start; after two hours it was 4·5 mm. and he could read comfortably. The improvement was maintained and no further eserine was required. This quite small dose of eserine was enough to restore the activity of the ciliary muscle and iris.

(*d*).—There is one result to record of the use of this method in an abnormal eye. A woman of fifty-two was admitted to hospital with a diagnosis of thrombotic glaucoma, after having used Ung. Atropinae 1 per cent. twice daily for seven days. The eye was hard and the pupil half-dilated. She was given eserine 2 per cent. to the eye three times on the day of admission and the pupil contracted. The tension also fell but this improvement was not maintained and she was later operated upon in an effort to save the eye.

(*e*).—A woman aged forty-three sustained accidental atropinization of an eye while at work. There was three-quarters mydriasis and the near-point was at 41 cm. One drop of eserine 0·5 per cent. produced miosis in thirty minutes and the eye was normal next day, the near-point now being 17 cm.

(*f*).—A technician accidentally introduced atropine into one eye. There was full mydriasis, which was counteracted by one drop of eserine 1 per cent. The eye was normal next day.

These results seem to indicate that the antagonistic effects of atropine and eserine on the eye are determined on a simple quantitative basis. This would explain the delay in the recovery of activity of the atropinized pupil which is rendered relatively insensitive to the normal concentrations of acetyl-choline present in the

eye. This insensitivity can be overcome by the administration of eserine which raises the acetyl-choline concentration.

A good deal of temporary visual disability results from the necessary use of atropine in ophthalmology and a kindness would be done to patients if they were given small doses of eserine, say 0·5 per cent. t.d.s. for forty-eight hours after atropine had been used for some relatively trivial ocular disease, or, in children, for refraction. Cycloplegia is a burden and we have here a method of enabling patients to resume close work considerably earlier than would otherwise be possible.

None of the observations here presented is original. It is interesting to speculate how the original description by Argyll Robertson was allowed to slip into the background and to give place to the constantly recurring statement—" eserine will *not* contract the atropinized pupil ".

Summary

The effect of eserine on a small number of eyes after the action of atropine is reported. In all cases contraction of the pupil and activity of the ciliary muscle were restored.

A possible therapeutic use for this action is suggested.

It is shown that these effects have been previously described, but have been neglected.

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NEW CONCEPTS REGARDING ANTERIOR DRAINAGE OF THE EYE *

BY

PAUL WEINSTEIN

Budapest

THE drainage system of the eye must play an important part in the aetiology of glaucoma. Little has been added, however, to the conceptions of Leber (1903) and Maggiore (1917), accepted for thirty years or more, until Ascher (1942) described the presence of aqueous veins in 27 per cent. of normal eyes. Goldmann (1946, etc.), working independently, discovered clear or striated veins in 75 per cent. of cases. Such vessels have been described or figured by Graves (1934), Loewenstein (1940), Thomassen (1947), Berliner (1948) and Davson (1949), and photographed by Gartner (1944)

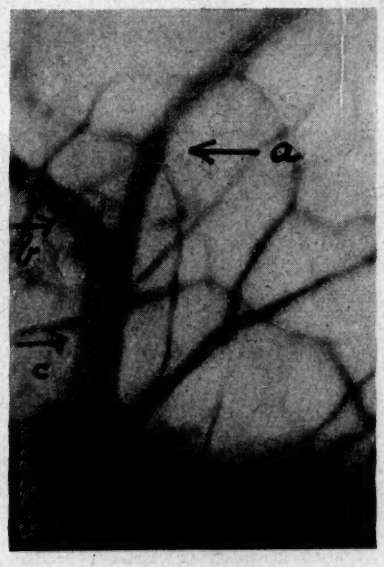

FIG. 1.—*a*, Vena aqueosa. *b*, V. recipiens. *c*, V. laminaris.

and de Vries (1947). The photographs reproduced for this paper were taken in my ward at the Ophthalmic Department of the Jewish Hospital, Budapest, in collaboration with my assistant, Dr. Forgács.

Fig. 1 shows an aqueous vein which runs an extended course to join an episcleral vein (v. recipiens) and proceeds as a laminary

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vein (v. laminaris) containing aqueous humour and blood in stratified layers. At first sight the laminary vein looks like two separate vessels, but if compressed, the entire vessel fills with

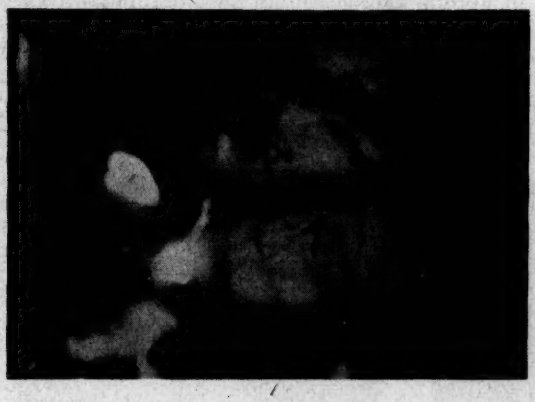
(*a*)

(*b*)

FIG. 2. — Negative glass-rod phenomenon or blood influx phenomenon. (*a*) V. laminaris. (*b*) Blood influx phenomenon after glass rod compression.

blood (Ascher's negative glass-rod phenomenon or blood influx phenomenon) as shown in Fig. 2. Our investigations suggest that aqueous veins eventually join the jugular, as compression of the latter produces the immediate appearance of blood, entering the aqueous vein in retrograde fashion (Fig. 3). If at the same

time the angle at the anterior chamber is examined gonioscopically, Schlemm's canal is also seen to fill with blood. The two systems are therefore in close communication.



(*a*)

(*b*)

FIG. 3.—(*a*) V. laminaris. (*b*) Blood influx after jugularis compression (Weinstein).

Ascher and Goldmann have called attention to the behaviour of aqueous veins in glaucoma. The result of the glass-rod test of Ascher and the apparent outflow pressure of Goldmann suggest that there is an obstruction situated somewhere in the region of Schlemm's canal. Our observations with the glass-rod test in the normal eye show that on removal of the obstruction from the

striated vein it quickly regains its former appearance but the process is delayed in cases of simple glaucoma because of the increased pressure in the efferent vein.

Visible pulsation of aqueous veins, which is comparatively common in normal eyes, signifies an uninhibited transmission to the efferent system of the undulations of the intra-ocular tension synchronous with the cardiac cycle, and the phenomenon is absent in glaucoma. We believe that when adrenalin decreases the ocular tension of glaucomatous eyes it does so by altering the diameter of the efferent vessels and thus reduces secretion but it does not

FIG. 4 (after Kiss).—*a*, Proc. ciliaris. *b*, Plexus ciliaris sec. (Kiss).

FIG. 5.—*a*, V. laminaris from limbus.

influence the calibre of the aqueous veins so that the outflow channels are relatively increased.

Francis Kiss, Professor of Anatomy at Budapest University, discovered in 1943 another efferent system. This consists of a thin plexus (plexus ciliaris sec. Kiss; see Fig. 4) adjacent to the within the region of the ciliary muscle. From it thin T-shaped veins and a few thick acutely-angled emissary veins branch off towards the episclera. Schlemm's canal normally contains aqueous humour only and so must aqueous veins at their origin. Those aqueous veins which appear at the limbus as laminary vessels (Fig. 5) are probably continuations of the thin veins of the ciliary plexus where the blood and aqueous must have mixed together. Fig. 6 demonstrates a thick emissary vein which was shown by serial section to arise in the ciliary plexus. We have discovered the episcleral continuation of such vessels, and Fig. 7

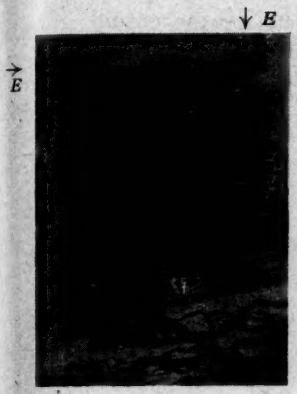


FIG. 6 (after Kiss) —*E*, V. emissarii.

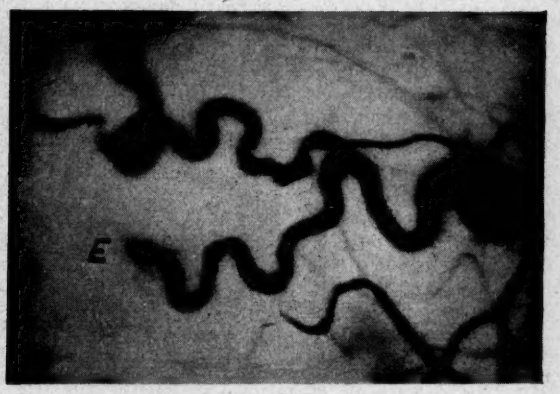


FIG. 7 (after Weinstein).—*E*, V. emissarii.

clearly shows such veins apparently arising from the sclera itself. Pressure with a glass rod showed that the direction of flow was away from the eye (Kaminskaya, 1948).

FIG. 8.—*E*, Emissarium in hydrophthalmos.

Busacca (1948) was unable to find aqueous veins in cases of hydrophthalmos and we had a similar experience in our own cases. But we discovered typical thick emissary veins with dilatations at the points of their emergence from the sclera (Fig. 8). It is well known that in cases of congenital hydrophthalmos, Schlemm's

canal is absent or replaced by tissue hyperplasia but yet the tension stabilizes at a moderate height. This suggests that a discharge system other than that of Schlemm's canal plus aqueous veins must exist.

The experiments of Seidel (1937) and later of Schulte (1948) and Kiss (1949) showed that some efferent veins were filled with indian ink while others remained unaffected. This work together

FIG. 9.—Emissarium cysticum (after Thiel).

with that of Schenk (1949) make the hypothesis of a second drainage system highly probable.

Dilated emissaries were described as early as 1928 by Thiel (Fig. 9), who believed along with Koeppe that emissary vessels were arteries. He emphasized that in cases of glaucoma with raised intra-ocular tension bulbous protuberances formed, containing aqueous humour and surrounded by pigmentation, at the place of emergence of the emissary vessels. Kaplan described conjunctival oedema around the dilated emissary vessels. We were able to confirm Thiel's findings and we frequently found in cases

FIG. 10.—Emissarium cysticum without vessel (after Weinstein).

of glaucoma an emissarium from which no vessels arose, and lying superficial to it a conjunctival cystic protuberance (Fig. 10). In normal eyes we frequently discovered dehiscences and foramina

Fig 5

FIG. 11.—Combined schema of the figures of Leber, Maggiore, Ascher and Kiss. *A*, V. aqueosa. *L*, V. laminaris. *E*, V. emissarii. *P*, preformed emissarium. *Ec*, emissarium cysticum. *Pr. c.*, processes ciliaris. *Pl. c.*, plexus ciliaris (Kiss). See Weinstein, 1949.

in the sclera from which no vessels emerged but which might act as preformed exit channels in cases of increased ocular tension.

Fig. 11 shows, concisely, the anterior discharge system of the

eye modified from Leber and Maggiore. Physico-chemical investigations of the aqueous humour suggest a considerable flow of intra-ocular fluid through the eye. Under these conditions, the Schlemm canal-aqueous vein system does not seem to be a sufficient means of egress. The venous system of the uvea as described above may be of greater importance and it may perhaps serve as a basis for future work on the aetiology and therapy of glaucoma.

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THE LABILITY TEST*

BY

T. L. THOMASSEN *and* W. LEYDHECKER

From the Institute of Ophthalmology, London, Director of Research, Sir Stewart Duke-Elder

THE lability test was described by Bloomfield and Lambert (1945). As with other provocative tests it is used for the detection of glaucoma in eyes with a normal pressure.

Methods

The test is a combined one. One hand is put into ice-cold water and at the same time constriction is applied to the neck in order to increase the venous pressure in the head. The latter is done by means of an ordinary sphygmo-manometer with the blood pressure cuff round the neck. We have only used a pressure of 40 mm. Hg. in the cuff. Bloomfield (1947) and Bloomfield and Kelterman (1947) use a pressure up to 60 mm. Hg., but many patients complain when such a high pressure is used and we have therefore reduced it. The test lasts only one minute and the ocular tension is measured with a Schiötz X-tonometer after half a minute, and after one minute. The rise in tension is recorded.

In some cases we have done the ice-water test and the neck compression test (the " cuff " test) separately, and then the combined lability test. In order to find out what really happens in the eye during the test, we have, in addition to measuring the ocular tension, also observed the aqueous veins and measured the pressure in an episcleral vein. This venous pressure is measured with a water manometer previously used by one of us and a fuller description of the method has been given by Thomassen (1947a). The water in the manometer is connected by rubber tubing to a transparent chamber, one side of which is composed of thin cellophane. This side is placed over the vein, which can be clearly seen through the transparent chamber, and the pressure required to collapse the vein is then read on the manometer.

We have examined normal eyes, and eyes suffering from simple glaucoma. In all, 52 normal persons have been examined. The ice-water test has been applied separately to thirteen of them. This test did not alter the pressure in the episcleral veins in any case, nor did the appearance of the aqueous veins change except in one case, in which a definite increase in the outflow of clear liquid was seen in the aqueous vein. This patient was the only one who had a definite increase in ocular tension during the test. This means that the increased intra-ocular pressure was combined with

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an increased outflow of aqueous humour and must therefore have belonged to that group of pressure changes which are compensated by the safety valve action of Schlemm's canal (Thomassen, 1949). This suggests that the rise in bulbar pressure was due to an increased amount of intrabulbar blood.

The " cuff " test produced a remarkable change in the aqueous veins in all thirteen cases observed. Both the blood veins and the aqueous veins increased in diameter, and the aqueous veins by degrees filled with blood. In some cases the flow in the aqueous veins remained in the same direction all the time while the contents altered; in other cases, however, the current was reversed and blood entered and filled the aqueous vein from the previous collecting vein. The amount of clear liquid usually decreased, but sometimes it increased considerably at first. This increased amount of clear liquid may depend on a pushing backwards of the clear liquid already present further along the vessels, but is more likely to depend on an increased outflow of aqueous humour. As mentioned before, such a rise in intra-ocular pressure combined with an increased outflow of aqueous is most probably due to an increase in the volume of intra-bulbar blood. This increase must therefore occur soon after the cuff is blown up and before changes in the episcleral veins are observed. The explanation may be that the venous obstruction affects the outflow in the vortex veins before the episcleral veins.

The pressure in the episcleral veins is preferably measured at or near the point where an aqueous vein joins a blood vein. We have found that the lateral pressure in these veins usually increases 20 to 30 mm. Hg. when the cuff is blown up to 40 mm. Hg. In a few cases we have found a smaller increase—the lowest was 12 mm. Hg.—and in a few cases a greater increase—up to 40 mm. Hg. These differences may perhaps depend on how the cuff is placed round the neck or on the varying degree of rigidity of the tissues and vessels in the neck.

In the combined ice-water and cuff test the same changes in the aqueous veins are seen as in the cuff test alone. The increase in venous pressure is also usually found to be similar, although in a few cases pressures slightly higher or lower were obtained with the lability test.

Results

As mentioned before, the ice-water test alone increased the bulbar pressure only in one case. In the other twelve the bulbar pressure was either unchanged or, as in a few, showed a slight drop. The cuff test usually produced about the same increase in bulbar pressure as the full lability test. Sometimes, however, a remarkable difference was observed, the higher pressure being produced as often by the cuff test alone as by the lability test.

The full lability test produced in 52 normal persons an increase in bulbar pressure of 0 to 8 mm. Hg., the average being 2·7 mm. Hg. Age was not found to influence the results of the test, the persons tested being from 12 to 75 years old.

How does the lability test produce the rise in bulbar pressure? It is obvious that the increased venous pressure will hamper the outflow of aqueous humour. The fact is, however, that we have found no correlation, either in normal or glaucomatous eyes, between the rise of pressure in the episcleral veins and the rise in the bulbar pressure. In our opinion, therefore, it is the increased blood volume in the eye which plays the most important part. The venous congestion produced by the cuff increases the blood volume in the eye, as in all probability does the ice-water test. It has also been shown (Bloomfield and Lambert, 1945), that the ice-water often increases the general blood pressure, which may account for its influence on the eye.

One phenomenon particularly shows that an increased blood volume is the most important factor—the fact that the pressure in the eye rises very rapidly during the test. After half to one minute it has reached its maximum and in a similar period after the test it has fallen to the pre-test value. Such a rapid change in the pressure can hardly be explained by an alteration in the amount of aqueous humour, especially in cases of glaucoma when the rise may be as high as 20 mm. Hg. or more.

Now an increased venous pressure in the episcleral veins must, of course, hamper the outflow through the aqueous veins. In order to investigate the effect of this acting in isolation on the bulbar pressure, we chose two normal persons who had no rise in the bulbar pressure during the cuff test. After a rest the cuff was blown up again in each case, but now only to 20 mm. Hg. The experiment lasted 20 minutes and the bulbar pressure was found to rise gradually and to reach a new level after about 15 minutes. In one case the bulbar pressure increased 8 mm. Hg., in the other 10 mm. Hg. When the cuff was first blown up the aqueous veins filled with blood, but after about 10 minutes aqueous was again visible, and finally, a new equilibrium seemed to be established between the venous pressure and the pressure in the aqueous veins. It was, however, impossible to determine whether the amount of clear liquid leaving the eye was the same as before the experiment started, as the veins now appeared considerably broader.

This shows that the effect of the increased venous pressure on the aqueous outflow does not make itself felt very much over periods as short as one minute. We have therefore come to the conclusion that it is mainly an increase in the intra-ocular blood volume that produces the rise in the bulbar pressure during the lability test.

The Lability Test in Glaucomatous Eyes

The lability test, like all provocative tests, has the disadvantage that a normal result by no means excludes glaucomatous disease. The question therefore arises—what is the cause of the abnormal reaction in glaucomatous eyes, and why is the test sometimes normal and sometimes abnormal in these eyes?

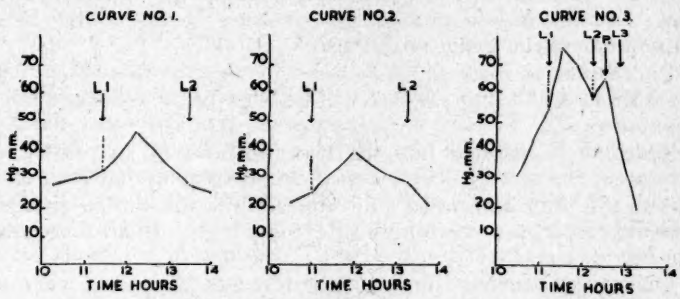
In most cases of simple glaucoma the pressure changes from hour to hour during the day and night. In our opinion therefore all research work on the ocular pressure in glaucomatous eyes must take into account whether the pressure is increasing, decreasing, or remaining level during the experiment. One of us has already shown that the venous pressure in the eye changes, and the appearance of the aqueous veins alters in a characteristic way when the ocular pressure is increasing or decreasing, Thomassen (1947a, b). It has also been found that another provocative test, the bulbar compression test, always gives an abnormal reaction when the bulbar pressure is increasing and a negative reaction when it is decreasing, Thomassen (1946).

We have therefore measured the ocular tension at half-hourly intervals during a large part of the day and repeated the lability test in the same eye many times. In this way it is often possible to estimate the phase of the ocular pressure during the tests. One has, however, to be very careful in deciding whether the pressure is increasing or decreasing at any particular moment. This difficulty has been mentioned before, Thomassen (1947a; 1946), but as it does not seem to have been fully understood, will be explained again.

Observation of the ocular tension cannot be continuous, and we can therefore never know with certainty how the pressure has changed between measurements. If, however, the following rules are obeyed the estimation can, in our opinion, be fairly accurate.

It is necessary to take at least three measurements—the first about half an hour before the experiment begins, the second at the start, and the third about half an hour after the experiment has finished. If these measurements show the same pressure, the experiment has been done while the intra-ocular pressure remained on the same level. If each succeeding measurement shows a rise, the experiment has been performed during an increasing phase; if each succeeding measurement shows a fall, the experiment has been performed during a decreasing phase. If the three measurements do not show such regularity, it is impossible to be sure in what phase the experiment has been performed. Thus many experiments will be performed in vain, since the readings of the ocular tension will often show no such regularity.

We have investigated fifteen patients suffering from bilateral simple glaucoma. Most of them were observed over many days, the ocular tension being measured every half hour. Five of the patients had a normal tension the whole time and showed no remarkable change. They had either been operated on or were being treated successfully with miotics. In these eyes the lability test always produced a rise in pressure within the limits found in normal eyes. In the other ten patients the ocular pressure changed during the time of observation. Curves 1, 2, and 3 show that the result of the test depends on whether the bulbar pressure is in an increasing or decreasing phase during the experiment.



Curves 1, 2, and 3 show the pressure of three different glaucomatous eyes during one day. The continuous line presents the bulbar pressure. L. means Lability Test. P. means that pilocarpine 2 per cent. is instilled into the conjunctival sac. The dotted vertical lines show the rise in pressure during the respective liability tests. Where no such dotted line is given below the test it means that the test has not produced any rise in pressure.

Curve 1 shows the results of a test performed while the ocular pressure was increasing. A rise of 11 mm. Hg. was produced. Two hours later the test was repeated, but now the pressure was decreasing and no rise was produced by the test.

In Curve 2 the same phenomenon can be seen. It should be noted that both tests were performed while the bulbar pressure was below 30 mm. Hg. Nevertheless, the first test, performed in an increasing phase, was positive, whereas the second which was performed in a decreasing phase was negative.

Curve 3 again shows a positive result in an increasing pressure phase. It is, however, impossible to be sure in which phase the second test was performed. As can be seen, the control measurements half an hour before and half an hour after the test show a higher pressure than that recorded at the starting point. Abiding by the previously mentioned rules, it is impossible to tell whether the pressure was in the increasing or decreasing phase

during the test. The third lability test in Curve 3 produced no rise in pressure. This test was done in a decreasing phase after the instillation of pilocarpine. The effect of pilocarpine on the lability test will be discussed later.

In all, the test was performed eight times during a definite increasing phase, and produced rises varying from 10 to 20 mm. Hg. and averaging 13·5 mm. Hg. The test was performed eleven times in the decreasing phase and on no occasion was a rise of pressure produced.

From these experiments we conclude that the lability test will be positive when the ocular pressure is in an increasing phase and negative when the ocular pressure is decreasing. In this connection the absolute height of the pressure seems to be of no importance to the result of the test.

Pilocarpine in itself seems to have no effect on the test. If the pressure is decreasing the test will be negative whether the fall is spontaneous or induced by pilocarpine. On the other hand, if pilocarpine is instilled into the eye and no drop in pressure is produced, the test will behave as if no pilocarpine had been used.

The test was performed four times while the bulbar pressure was increased but remaining on the same level. In all these cases the test was positive.

On many occasions, however, the test was performed when the pressure remained level and at a normal height. In these cases the test was sometimes positive and sometimes negative. When the pressure was studied in greater detail over many days it was found that all the eyes which showed a negative test were very well stabilized at a normal pressure. Five of our patients, as mentioned before, belonged to this group and no abnormalities were ever found in their pressures.

On the other hand in five cases showing a positive test, although with level pressures within normal limits, investigation showed that the ocular pressure in these cases was very unstable. In four of them the pressure had been increased a few hours earlier, and in the fifth case the pressure had been increased the day before the test.

From our findings we can make the following summary. The lability test will be positive if the ocular pressure is increasing, negative if it is decreasing, positive if it is increased and remaining on the same level, negative or positive if the pressure is normal and remaining on the same level.

If in the latter case it is positive, the bulbar pressure is probably unstable. This explains why the test is of such limited value, and we agree with Sugar (1948) when he emphasizes that repeated measurements of the pressure will be at least as valuable as the test.

It is of some interest that our findings on the lability test in glaucomatous eyes are the same in detail as one of us has found using another provocative test, namely the bulbar compression test, Thomassen (1946).

It has already been emphasized in this paper, that the rise in the ocular pressure produced by the lability test must be one mainly to an increased blood volume in the eye. In cases of simple glaucoma we have seen that the same eye may respond very differently to the tests applied. That is to say that sometimes the vessels of the eye dilate considerably to accommodate the increased blood volume and sometimes they are able to resist the stress and do not dilate at all. The explanation must be that the reactions of the vessels vary. Normally they will be in a state when they dilate a little. In the increasing phase in glaucoma they cannot withstand the stress as they normally do and they dilate considerably more. In the decreasing phase they are better able to withstand the stress and do not dilate at all.

With our present knowledge we are ignorant of the nature of these vascular changes, but it is possible that they represent the actual cause of the glaucomatous disease. It is certainly probable that they cause the variations in the venous pressure which have been described previously, Thomassen (1947a).

Summary

It is found that the lability test in normal eyes raises the ocular pressure from 0 to 8 mm. Hg. The rise must mainly be caused by an increased blood volume in the eye.

In eyes suffering from simple glaucoma the test will be positive if the ocular pressure is in an increasing phase and negative if it is in a decreasing phase. The test will be positive if the pressure is high and remains on the same level, but it can be positive or negative if the pressure is normal and remains on the same level. If the test is positive under the last mentioned circumstances, the bulbar pressure is presumed to be unstable.

The lability test can therefore change from positive to negative or *vice versa* in the same glaucomatous eye within a short interval. The cause must be that the conditions in the ocular vessels change. The nature of such changes is unknown, but it is possible that they represent the actual cause of the glaucomatous disease.

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WHITE RINGS IN THE CORNEA*

BY

S. J. H. MILLER AND W. H. GORDON

London

MR. W. H., a grocer, aged 66, was admitted to the Moorfields, Westminster and Central Eye Hospital, London, on January 19, 1948, suffering from a sarcoma of the choroid in the lower nasal quadrant of the right eye. This eye also presented a number of well-marked white corneal rings; the clinical picture is reproduced in Fig. 1. Examination of the left eye, which was otherwise

FIG. 1.—Right Eye.

normal, disclosed four faint corneal rings, shown in Fig. 2 (a). Fig. 2 (b) shows one of these rings in the optical section of the slit-lamp beam, apparently situated in the substantia propria. The patient gave a history of having been involved in an accident some 30 years previously, in which a carbide installation exploded and spattered both his corneae with gritty particles. After a few weeks of discomfort his eyes were symptomless and remained so until three weeks before admission when he noticed a defect in his right field of vision, together with a deterioration of visual acuity.

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The right eye was excised three days later and sections were stained by haematoxylin and eosin. The chief point of interest is the situation in depth of the deposits, which in cases previously reported have been on, in, or immediately under, Bowman's membrane. As will be seen from the low-power photomicrograph (Fig. 3) they are nearly all in the middle two-fourths of the stroma, though a few outlying ones (Fig. 4) are just below Bowman's membrane, the deep aspect of which they invade.

A thin meniscus, concave forwards and incomplete at one part of its margin, marks the deep boundary. The remaining deposits are within the concavity of

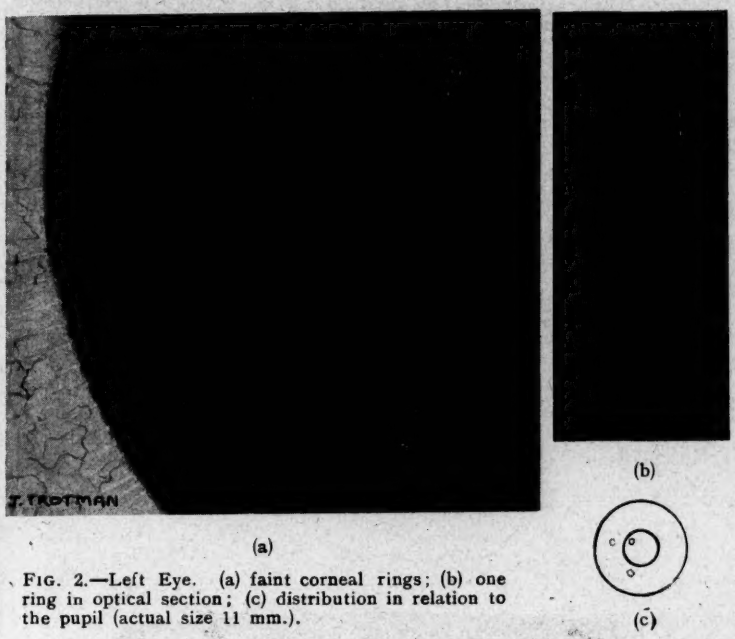

FIG. 2.—Left Eye. (a) faint corneal rings; (b) one ring in optical section; (c) distribution in relation to the pupil (actual size 11 mm.).

this meniscus, and the larger ones tend to form imperfect rings with scalloped borders, some of these rings being in their turn arranged in roughly oval formations. This latter configuration is most strikingly shown in the central large deposit which is the subject of the high-power photomicrograph (Fig. 5).

The higher magnifications show the meniscus to be composed of fine dust-like particles situated within, and also between, the corneal lamellae. These stain blue with haematoxylin. The other formations have a similar fine structure but in addition there are many larger particles staining a dark purplish blue. The staining reaction suggests that calcium is present in the particles forming the deposits.

Interest in this condition dates from a description of three cases by George Coats (1912), who suggested a congenital aetiology. Ballantyne (1933) described six cases, and he thought that white rings may be secondary to intra-ocular disease. MacRae (1935) maintained that such cases were probably traumatic in origin. In our own case, a traumatic aetiology seems most probable, and we suggest that the depth of the lesions is related to the degree of

trauma. The type of corneal ring usually described, situated in the plane of Bowman's membrane, may be the product of a very minor and therefore unnoticed injury.

FIG. 3.—Low-power photomicrograph of cornea.

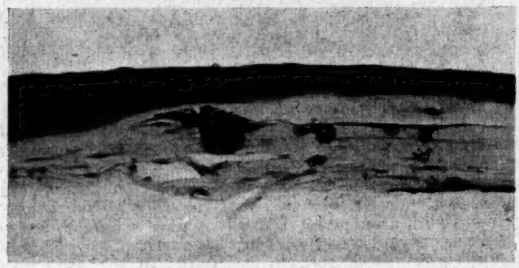

FIG. 4.—Photomicrograph of Bowman's membrane.

We are indebted to Mr. P. McG. Moffatt and to Mr. Eugene Wolff for their help, and for permission to publish this case.

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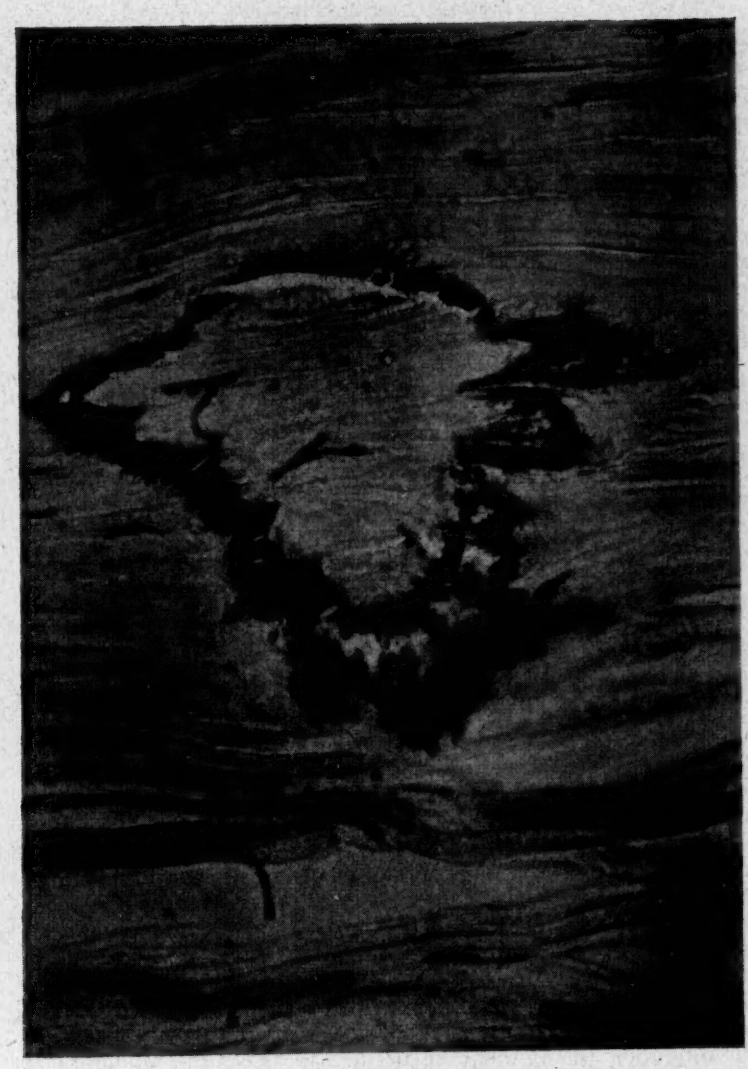

FIG. 5.—High-power photomicrograph of central deposit.

INDUCED PUPILLARY OSCILLATIONS*

BY

F. W. CAMPBELL AND T. C. D. WHITESIDE

From the Institute of Physiology, University of Glasgow

THE ease with which the iris can be observed, combined with the long course of the nervous pathways, accounts, in great measure, for the extensive literature on pupillary reflexes. Much of this work has been undertaken by clinicians seeking guidance in diagnosis. Yet, in most present-day investigations, use is made of complex apparatus which is far from suitable for use in routine clinical examination. It was therefore with some interest that we noted that Stern (1944) had briefly described a simple technique for investigating pupillary activity.

If a slit-lamp is adjusted so that the vertical image of the slit falls on the edge of the iris and just overflows into the eye and on to the retina, the pupil becomes smaller after a short latent period. As a result, the beam of light is partly or completely cut off from the retina, and the pupil then enlarges to near its previous size. The retina, being re-exposed to light by this dilatation, again initiates a reflex contraction of the iris, and the cycle of events is repeated. In this way it is possible to set up sustained, and easily observed, oscillations of the iris. As a result of these oscillations the retina receives a series of light stimuli whose frequency and duration is dictated by the behaviour of the iris. The frequency and duration of the oscillations depend on: (1) the latent period of contraction of the iris; (2) the duration of the contraction; (3) the latent period of dilatation of the iris; (4) the duration of the dilatation. The frequency of the oscillations is such that the latent period of contraction must encroach on the dilatation phase, and the latent period of dilatation must encroach on the contraction phase.

Loewenstein and Friedman (1942), and Loewenstein and Schoenberg (1944), using pupillography in the examination of early unilateral glaucoma and neuro-syphilis, observed, in consecutive pupillary contractions, a prolongation of one or more of the above periods in all except in the first few successive contractions of a series. Such a change, if it is sustained, should be interpreted also, and more simply, as a change in the frequency of induced pupillary oscillations. As a preliminary to a clinical investigation it was therefore decided to assess the reliability of the technique on normal subjects under the various conditions likely to be met in clinical work.

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Apparatus and Method

The observations were carried out in a dark room: we used a Gullstrand clinical slit-lamp, which, to stabilize the conditions under which the experiments were performed, was fed from a constant voltage transformer, and the light output checked from time to time with a photometer. The slit of the slit-lamp was at maximum aperture. The pupil margin was observed by means of a biomicroscope with low-power objectives. A chin- and forehead-rest steadied the subject's head, and fixation movements were greatly reduced by placing before the subject's right eye a small adjustable mirror, in which he could fixate the reflection of the faintly glowing filament of a 12-volt car-lamp about five metres away. The oscillations were timed by means of two stop-watches calibrated in fifths of a second.

The subject was comfortably seated, and the mirror before his right eye adjusted to make the fixation point appear to be directly in front. In each of the experiments the slit-lamp was placed so that the angle of incidence of the light on the subject's eye was 30° to 45° to the temporal side of the optical axis of the left eye. The image of the slit was brought to a focus on the iris. The pupil margin was then observed through the binocular microscope, and the light brought to the edge of the iris until it just entered the pupil. As soon as a regular oscillation had become established, one stop-watch was started during the contraction phase of a cycle, and ten complete oscillations were timed. The watch was then handed to a clerk who recorded the reading to the nearest fifth of a second, while the observer continued his observations with a second stop-watch. Ten groups of ten contractions were usually timed in continuous series. From time to time during a period of observation there were involuntary eye movements. In such cases timing was stopped, and only resumed when the " hippus " was re-established. It was found most suitable to measure the time taken for ten complete oscillations. This time was converted into frequency of contraction per minute.

In many instances a 16 mm. cinematograph film was made of the oscillations by means of ultra-violet light and panchromatic film. This allowed direct measurements to be made on the amplitude and frequency of the iris movements.

Results

Position of the slit of light on the iris.—After some trials at inducing this pupillary oscillation it was noticed that the position of the slit of light on the iris appeared to influence the frequency and amplitude of the oscillations. In order to estimate the effect of the position of the light, readings were taken with the light alternately

just at the pupil margin and then further towards the centre of the pupil.

With the slit of light placed centrally, the oscillations were irregular in frequency and amplitude, and consequently difficult to count. With the light just overlapping on to the pupil, however, the frequency was regular, of good amplitude, and well sustained. In the subsequent experiments, care was taken to have the light at the pupil margin.

Fatigue.—Fatigue of the light reflex has been demonstrated by Lowenstein and Friedman (1942). They found that, with a recurrent light stimulus of one second duration every three seconds, the iris excursion began to diminish after the fifth stimulus, the effect developing gradually until, after the sixtieth stimulus, there was almost complete immobility of the iris. The light response of this immobile iris could be restored by a psychosensory stimulus such as a sudden sound, or the suggestion of fear or pain. Among the changes in the pupillogram ascribed to fatigue were diminished amplitude of contraction and dilatation of the iris, and prolongation of the latent period of contraction up to 0·4 second. Fatigue of such rapid onset would be expected to show in our observations, where 100 oscillations usually followed in a continuous series. We found no falling-off in frequency, such as might have been expected if the latent period of contraction had been prolonged to 0·4 second from the normal one of 0·2 second. There was no obvious decrease in the amplitude of the oscillations.

To make assurance doubly sure, a special series of observations was made on both experienced and inexperienced subjects. Here silence was observed, and up to 200 continuous oscillations were directly scrutinized. Again, fatigue was not manifested.

Effect of Preliminary Dark Adaptation.—For the purpose of the experiment a sufficient degree of dark adaptation was obtained by seating the subject (N.A.) in almost complete darkness for a period of thirty minutes. At the end of this period the subject was placed at the slit-lamp, and observation was begun. On receipt of a visual signal, made automatically every thirty seconds, the observer began timing ten oscillations. In the short interval after the timing of these ten contractions, during which the next signal was awaited, the beam of light was directed away from the subject's eye.

Fig. 1 shows the results of two of these experiments performed under identical conditions. It will be seen that during the first five minutes the rate fell from about 85 to a steady mean of 73 oscillations per minute. After dark adaptation the beam of the slit-lamp brought about marked miosis. This miosis wore off in several minutes as light adaptation proceeded.

Effect of Preliminary Light Adaptation.—A sufficient degree of light saturation was obtained by seating the subject (N.A.) with the forehead against an opal X-ray viewing screen for a period of 10 minutes. The screen was illuminated from behind by a 250-watt lamp. Immediately this period of light adaptation had been completed, observations were begun and recorded as described above.

In this series, at the beginning of each observation, the pupil was wider than normal, the amplitude of the oscillations was

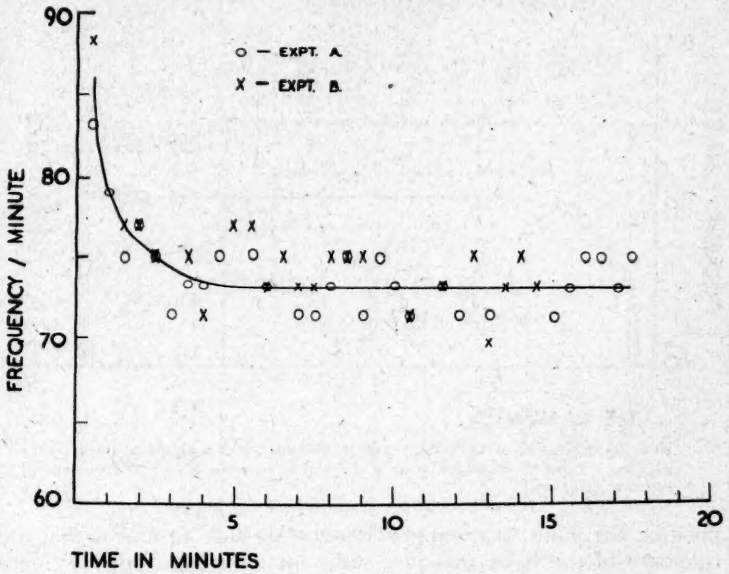

FIG. 1.—Effect of light adaptation on the frequency of induced hippus. Time in minutes after a preliminary period of 30 minutes dark adaptation.

smaller, and some difficulty was encountered in inducing the oscillations. Presumably because of these factors, the readings obtained showed a greater scatter about the mean as compared with those illustrated in Fig. 1. The means of three such experiments are shown in Fig. 2. During the first five minutes the rate increased from 60 to 70 oscillations per minute; it remained at this level until the end of the observations.

It will be noted that in the two previous experiments there is no indication that pupillary fatigue is affecting the rate of induced oscillations, even after fifteen minutes' observation.

Effect of Altering Light Intensity from the Slit-lamp.—To investigate the effect of changes in light intensity on the frequency of the pupillary oscillations, a means was required of effecting rapid and predetermined changes in the light intensity of the slit-lamp beam. A delay in effecting this change might have allowed retinal adaptation to modify the results obtained. We therefore introduced into the low-voltage supply to the lamp, a variable resistance which was connected to a two-way foot-switch. The resistances were adjusted so that in one position of the switch the lamp was being overloaded by 20 per cent. of its rated voltage, and in the other

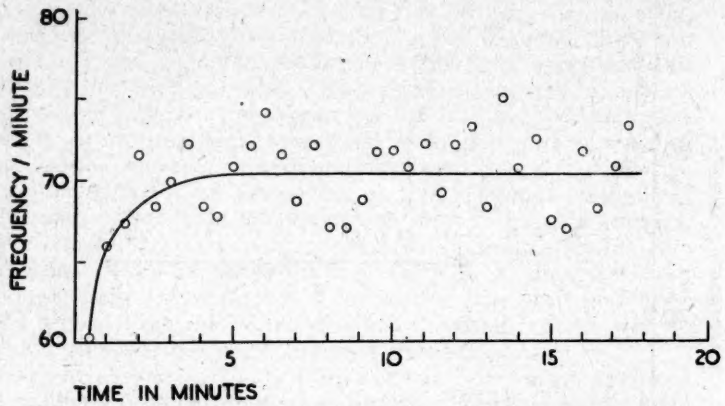

FIG. 2. Effect of relative dark adaptation on the frequency of induced hippus. Time in minutes after a preliminary period of ten minutes light adaptation.

position the lamp was being under-run to such an extent that the intensity of the light was just sufficient to induce pupillary contractions. As measured by a barrier-layer photo-electric cell, the light intensity in the second position was 6 per cent. of that in the first. This range of experimental conditions far exceeds that likely to occur as a result of mains voltage fluctuation during clinical work.

The subject (T.W.) was dark-adapted for a period of 5 minutes, A series of twenty readings, each of ten oscillations, was then made, during which the light intensity was alternately high and low. In this way the effect of any retinal adaptation that might occur fell equally on each group. The results obtained during low-intensity illumination had a mean of 61·5 oscillations per minute as compared with the mean of 70·1 oscillations per minute during high-intensity illumination. The " t " test applied to these

results showed a significant difference in the means at the 1 per cent. level of significance.

Correlation of Pupil-Size and Frequency of "Hippus."—From the previous experiments we had formed the impression that the frequency of the oscillations induced was higher when the pupil was small than when it was large. The relationship of frequency of

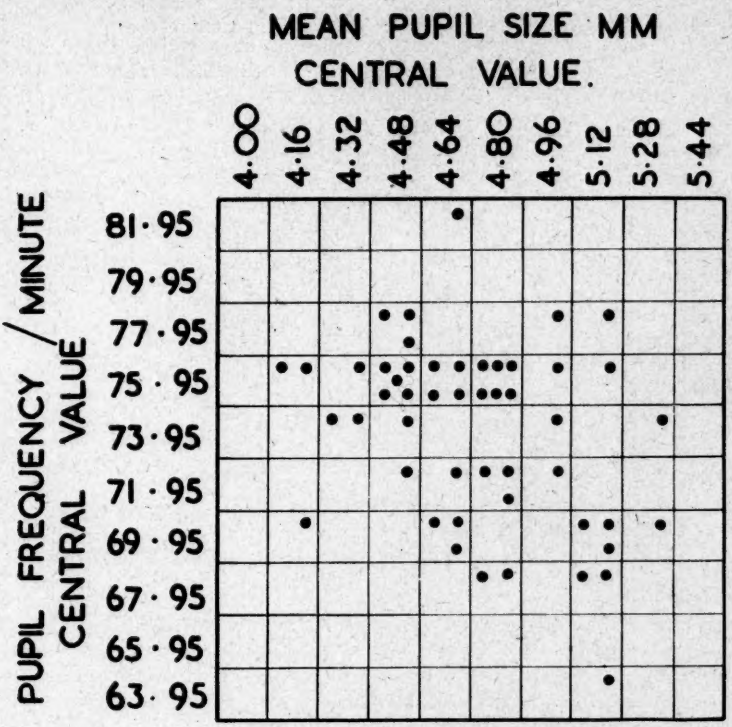

FIG. 3. Correlation between the frequency of induced hippus and simultaneously noted pupil size in one subject.

oscillation to pupil-size was therefore investigated. A graticule eyepiece was used to make an estimate of pupil-size while ten oscillations were being timed. This approximation in the measurement was inevitable, as one figure had to represent the mean pupil-size during the ten oscillations counted. It was decided to make the measurement at the maximum period of dilatation while the pupil was in hippus. The graticule scale was read to the nearest quarter of a division, 0·16 mm. of actual pupil-size. In Fig. 3 the

mean frequency during each group of ten oscillations is plotted against the estimated mean pupil-size. For the fifty observations made, the correlation ratio of 0·309 is significant; that is, an increase in pupil-diameter is associated with a decrease in the frequency of the oscillations.

Inaccuracies inherent in this method may account for the results which lie outside the general trend. Further investigations are being made with the help of cinematography.

The Effect of Exercise.—There was a possibility that the differences observed in the experiments on light and on dark adaptation might be due in part to the fact that during dark adaptation

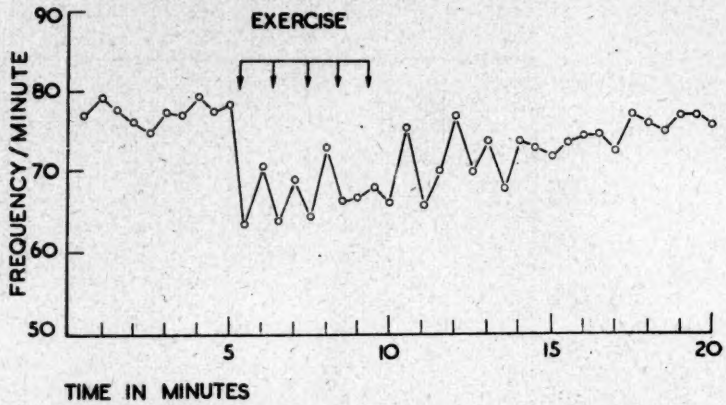

FIG. 4. Frequency of induced hippus after five short periods of exercise. The mean results of two experiments are presented.

the subject had been physically at rest for a period of 30 minutes, whereas, during light adaptation, the period of rest was only of 10 minutes. As an indication of the extent to which this initial resting period might be responsible for changes in the rate of the oscillations, the effect of exercise was investigated.

The exercise consisted of stepping up and down from a chair six times. As an initial trial showed that the effect was apparently transient, the exercise was repeated at stated intervals during the course of the experiment. In order to allow the subject to settle down, and to eliminate the effect of previous retinal adaptation, readings were made every 30 seconds for five minutes before exercising, a steady mean thus being reached after two or three minutes. The mean results of two experiments are shown in Fig. 4. Moderate exercise produced a rapid drop in the frequency of the oscillations. Soon after the exercise stopped, the frequency

began to return to its normal level at rest and reached it in about 10 minutes.

Examination of a group of normal subjects.—Thirty men and thirty women were examined under constant conditions. The total number was confined to sixty as, in the available subjects, the range in ages was not sufficiently wide to permit an accurate examination of a possible correlation between oscillation frequency and age. In this experiment, the age of the majority of the subjects was between 19 and 25 years with extremes at 17 and 36 years. These subjects—mostly medical students—were healthy, and with no complaint apart from a refractive error of moderate degree in a few cases.

The iris colour was noted, and, in addition, in 37 subjects the pulse-rate was taken immediately before and immediately after observing the pupil, the mean pulse-rate being noted. No significant difference was found in the frequencies observed in men and

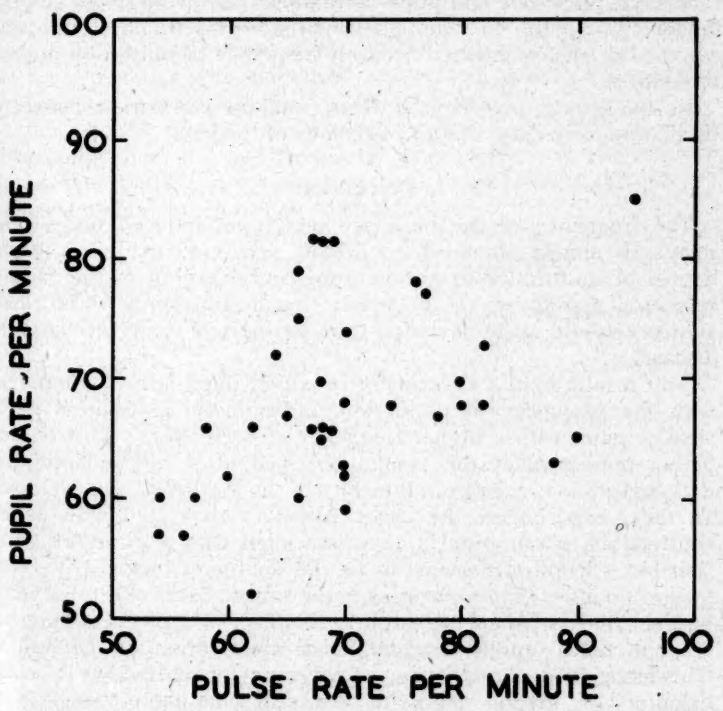

FIG. 5. Correlation between the frequency of pupil oscillation and of resting pulse in 38 subjects.

in women. In the complete group, the mean frequency was 68·9 oscillations per minute and the standard deviation was 11·3 oscillations per minute. In the 37 subjects whose pulse-rate was also noted, a positive correlation was found between this rate and the oscillation-frequency of the pupil (Fig. 5). This data gave a positive correlation ratio of 0·408 which is significant at the 1 per cent. level.

The frequency of pupillary oscillations thus appears to be positively correlated with the heart-frequency in a group of subjects. From experiment on exercise, however, we know that in a person subjected to moderate exercise the rate of oscillation decreases, whereas the pulse-rate increases. It seems therefore that, if such a correlation exists in the individual, it is readily broken down by any external stimulus, such as exercise, which causes pupil-dilatation and increase in heart-frequency.

One subject was examined on several occasions over a period of four days, pulse-rate and pupil-oscillations rate being noted simultaneously. In the 45 readings which were taken, no significant correlation was established between frequency of pulse and pupil-oscillation.

In the group investigated there was no correlation between oscillation-frequency and age or colour of the iris.

Discussion

The frequency of the pupillary oscillation induced under our relatively simple standard conditions seems to exhibit a high degree of uniformity in normal subjects belonging to the rather restricted age-group, 17-36 years. Such uniformity in normal subjects should make deviation from the normal easily detected in disease.

The results of the experiment in which pupil-size is compared with the frequency of oscillation, indicate the association of a smaller pupil with a higher frequency of oscillation. This observation may explain the results obtained after light-adaptation, dark-adaptation, change in intensity of the slit-lamp, and exercise. In these experiments the factor which is associated with fewer contractions per minute is also associated with a pupillary constriction. Pupil size seems to be the dominant factor. We can hazard no more than a guess as to the cause of this effect. It may be that the iris, when the pupil is small, is in a physical state to respond more rapidly to changes of illumination of the retina. This association of pupil size and frequency of contraction is being examined in greater detail by means of cine-photography in a further investigation.

The absence of fatigue is striking and in direct contradiction

to the findings of Loewenstein and Friedman (1942). The discrepancy may be due to differences in technique.

It should be noted that the iris can contract more rapidly than it does under the conditions of the present work. Bartley (1942) found that the iris could respond to short-duration stimuli, individual contractions of the iris being obtained for frequencies of up to 180 stimuli per minute. At higher frequencies no oscillation occurred.

Summary

1. When the beam of a slit-lamp falls on the iris and overlaps on to the pupil to reach the retina, a sustained series of iris oscillations takes place.

2. For reliable results it is necessary to adjust the slit so that the beam just encroaches on the pupillary margin. If the beam falls near the centre of the pupil the rhythm of the contractions becomes irregular.

3. Previous dark-adaptation of the retina causes an increase in the rate of these oscillations during the first five minutes of adaptation to light stimulation.

4. Previous light-adaptation causes a decrease in the rate of the oscillations during the first five minutes.

5. Sudden and marked changes in the light intensity of the slit-lamp affect the pupillary rate. An increase in the intensity causes an increase in the oscillation rate; a decrease in the intensity causes a decrease in the oscillation rate.

6. Exercise of the subject shortly before beginning the test causes a decrease in the rate of oscillation, possibly as a result of pupil dilatation.

7. A significant negative correlation is found between pupil-size and frequency of oscillation. It is suggested that the effects of light- and dark-adaptation, light intensity, and exercise may be explained on the grounds of their effect on pupil size.

8. Age, sex, and colour of iris do not significantly affect the frequency of pupillary oscillations.

9. A significant positive correlation is found between resting pulse-rate and frequency of pupillary oscillations in a group of normal subjects.

10. Pupillary fatigue does not significantly affect the frequency or amplitude of the oscillations.

We are indebted to Professor R. C. Garry for his advice and encouragement, and to Professor W. J. B. Riddell for apparatus. The cost of this investigation was defrayed by the Rankin Medical Research Fund.

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AFTER—IMAGES*

BY

R. WEALE

From the Vision Research Unit, Medical Research Council, Institute of Ophthalmology, London

EDRIDGE-GREEN (1945) has described some experiments on the persistence of vision, which appear to him to give evidence (*a*) that the rods are not percipient elements but gland-like structures, secreting visual purple; (*b*) that the cones are not stimulated directly by light but indirectly by the decomposition products of visual purple; (*c*) that visual purple is secreted into a space filled with fluid, in which the tips of the cones are immersed; (*d*) that under certain circumstances relative movement can take place between this fluid and the tip of the cones. The writer has repeated and extended Edridge-Green's experiments in order to test the validity of the above conclusions.

It would appear that Edridge-Green did not differentiate between foveal and extra-foveal vision. Thus he mentions a strip of white paper (3 in. x $\frac{1}{4}$ in.) placed on a black-board, and describes the fate of the positive after-image resulting from a quick glance at the strip of paper, but omits to state the distance he viewed it from. In another experiment he mentions the after-image due to a red flower seen at a distance of 3 metres; in this instance it is reasonable to assume that it was cone-vision which predominated over rod-vision. The importance of distinguishing between the two kinds of vision is brought out forcibly by a variation of Bidwell's well-known experiment.

Methods

A disk of white cardboard, one half of which is painted black, has a small hole (1 cm. diameter) drilled in that boundary where white follows black on rotating the disk. A steel mirror to which is clamped a red filter is placed behind the disk. A small bright filament lamp is placed in front of the disk so as to illuminate it, and is so adjusted that the filament can be seen in the mirror when the aperture is in the correct position. The hue will, of course, be red. A wedge is forced between the mirror and the filter so that reflections at the two surfaces of the latter cannot interfere with the observations. If the observer is at such a distance that the image of the filament does not subtend at the eye an angle larger than 1·5°, the hue will remain red even if the motor-driven disk is rotated. However, if the observer fixates a point 3 or 4 cm. to one side of the image, the hue changes to green. This colour can also be observed on increasing the visual angle by a lens during direct fixation.

It is thus seen that, at least as far as negative after-images are concerned, a difference must be made between foveal and extra-

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foveal vision. Further, if (*a*) were correct it might be expected that the intensity of the red sensation would be diminshed extra-foveally, without any marked change in hue taking place.

The next experiment was designed to test the movements of after-images. A black cardboard disk had a small hole (about 1 cm. diameter) drilled into it, and was fixed to the motor as before. On the far side the aperture was covered with white translucent paper which was illuminated with a microscope lamp. The observer sat at a distance of about three feet from the disk, and electrically controlled the flashing of the light brought about by the passage of the aperture in front of the lamp. There was the faintest background illumination, rendering fixation possible. To test Edridge-Green conclusion (1946) regarding the function of the eye-muscles in effecting the disappearance of the after-image by exerting pressure on the eyeball, the eyes were moved after the flash had taken place, care being taken that no light should fall on the exposed parts of the eye; these as all other observations were monocular. When vision was foveal the after-image disappeared instantaneously: this is in agreement with Edridge-Green's result. When, however, vision was extra-foveal movement of the eyes did not affect the after-image. Of the red, green, and yellow filters used, the last rendered the observation of the effect more easily than the other two, probably on account of the higher luminosity.

In another set of experiments an ordinary torch was used for stimulation. It was focused so as to form a beam as nearly parallel as possible. The bulb and its *reflector were viewed in a dark room, the appearance being that of a bright ring* surrounding a dark one, at the centre of which there was the small bright filament, which formed an admirable fixation point. Red, yellow, and green filters were used, giving similar results, provided the brightness was not too intense. For example, when the filament had been fixated from a distance of about five feet for roughly ¼ to ½ minute, and the torch was turned off, the positive after-image of the *reflector* appeared immediately, but that of the *filament* could not be seen at all. (This explains the apparently rapid disappearance of the after-image in the first part of the previous experiment.) When the light in the room was switched on, the after-image of the reflector of course, became negative, and that of the filament remained invisible. In order to determine whether the after-image moved relatively to the retina the point of intersection of two thin black lines was fixated. Owing to the tendency to look at the after-image—naturally with the fovea—it appeared to move: it follows that it seemed to move in the direction in which the eye was turning. However, by making a great effort in fixating a given point in the visual field, the observer could not detect any movement of the after-image. As soon as he relaxed his concentration the after-image moved. Repeating the experiment one evening when tired, the observer found it impossible to keep the after-image still.

Edridge-Green also mentions the distortion (" bulging ") of the after-image when the closed eyes are rotated right or left. The after-image which he used for this experiment was due to the strip of paper mentioned above.

The present writer repeated the experiment, viewing the strip from about two feet, but could not obtain a conclusive result. On another occasion, however, he viewed a complex object consisting of a gothic window in a church. The window, illuminated by the sun from the far side, subtended an angle of about 7° at the observer's eye. On closing the observing eye, he could see an exact positive after-image of the window; it became negative on opening it, positive on closing the eye again, etc. Details could be detected in this image which had escaped the observer's attention in the original, but were subsequently found to be there. It should be noticed, however, that the fixation point, a yellow cross on a red background, could not be seen in the after-image. The writer moved his eyes about, and found that the image became deformed only when its general dissolution had become advanced.

The long and detailed persistence of this large image would be unlikely if the retinal fluid moved relatively to the receptors. The fact that the coloured fixation area could not be seen is in agreement with the observations made by other workers (Duke-Elder, 1932). Its importance in connection with colour-matching is obvious.

These results are at variance with Edridge-Green's conclusions, in particular with his statement that the cones are stimulated indirectly by the decomposition products of the photochemical fluid (visual purple) and not directly by light. On the contrary, they suggest that in cone-vision the response is more rapid than in rod-vision. They also suggest that the persistence of the stimulating action is greater in the latter.

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COMPLICATION OF TRAUMATIC HYPHAEMA*

BY

J. A. N. LOCK

Surgeon Lieutenant Commander, R.N.

HYPHAEMA is a common sequel to injury of the eye, whether perforating or non-perforating. Most cases subside without further incident, but secondary glaucoma must always be regarded as a possible complication.

Miss A. B., aged 14 years, received an injury to the right eye from a paper dart on August 18, 1948. The vision of the eye was immediately lost. She was examined on the following day, and the findings were:—*Right eye*, vision 6/12, conjunctival and ciliary congestion, and 3 mm. hyphaema; semi-dilated, fixed, pear-shaped pupil; fundus details not seen. *Left eye*, vision 6/5, no abnormality. She was admitted to hospital, and atropine was instilled into the right eye. On August 22, 1948 a further haemorrhage occurred into the anterior chamber of the right eye, and was followed by a rise of intra-ocular tension. Atropine was stopped and eserine drops instilled, while magnesium sulphate gr. ii was given by mouth twice daily. The blood-count at this time was normal, and the bleeding and clotting times were normal. On August 24, 1948, after a fall, the tension rose again, but was reduced by liq. adrenalin hydrochloride, 1/1000, minims 5, injected subconjunctivally. On August 27, 1948, the tension again became raised but was controlled by guttae adrenalin hydrochloride 1 in 50, instilled 4-hourly. On August 30, 1948, the tension was again high, and the vision was reduced to hand movements. Paracentesis of the anterior chamber was carried out under pentothal anaesthesia, and a large quantity of blood-clot was evacuated. Subsequent improvement was steady, and she was discharged from hospital on September 18, 1948. Examination on October 12 showed that the right pupil was semi-dilated and pear-shaped. The eye was otherwise normal, and its vision 6/12.

It is suggested that there is considerable risk of secondary glaucoma if a mydriatic is employed in cases of post-traumatic hyphaema, because dilation of the pupil may re-open a bleeding point in the iris. Such glaucoma will be more readily controlled if homatropine rather than atropine has been used.

I wish to thank Surgeon Captain T. N. D'Arcy, R.N., for permission to publish this case.

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CENTENARY OF HJALMAR AUGUST SCHIÖTZ

ON February 9, 1950, one hundred years after his birth, a statue of the late Professor Schiötz was unveiled at the Oslo University Eye Clinic by Norwegian oculists. Having graduated in 1877, Schiötz worked at the Rikshospital for about two years, and then proceeded to study ophthalmology under Fuchs in Vienna and Javal in Paris. It has been aptly stated in Norway that Schiötz, with his lively

HJALMAR AUGUST SCHIÖTZ

intelligence, was thus enabled to absorb German thoroughness together with Gallic dexterity of thought. He assisted Javal in making the ophthalmometer, attended congresses in London and Milan, and returned to Oslo in 1881. Two years later he was awarded the M.D. degree for a thesis dealing with certain optical features of the cornea.

Schiötz became the first Norwegian professor of ophthalmology in 1901. Before that date he had made a self-registering perimeter as well as a modified ophthalmoscope, and he now proceeded to evolve the famous tonometer. It will be recalled that he was a

resourceful craftsman, and that models of all these inventions were fashioned by his own hands in the workshop built on to his home. As time went on, the demands of teaching, writing, and private practice precluded him from much personal contact with his colleagues abroad, but his fame spread far and wide.

One keynote of Schiötz's character was an intellectual austerity which made him eschew the plaudits of the multitude. Showmanship he despised, but his personal integrity, linked with clinical acumen and skill in surgery, built for him a vast reputation among ophthalmologists all over the world. The memory of his inventiveness is linked with an eponymous tonometer, but the people of Norway revere the name of Hjalmar August Schiötz chiefly for spiritual qualities, which endure longer than any machine.

OBITUARY

ROBERT ERIC HENRY

ROBERT ERIC HENRY died suddenly in London on January 11, at the age of 51. He hailed from Sydney, Australia, where he began his medical career in 1915. After completing his first year of medicine he enlisted for war service abroad, and served with the A.N.Z.A.C. for 3 years (1916-19), receiving a knee wound while fighting in France. In 1919 he returned to his interrupted medical studies, graduated in 1923 and eventually travelled to England in 1930 for the purpose of specializing in ophthalmology.

While in London he contracted poliomyelitis, which resulted in a crippling paralysis of both legs. After 3 years' treatment he returned to London in 1935, barely able to stand erect or to walk even a limited distance with leg calipers and his two sticks. Nevertheless he consistently rejected any kind of commiseration, and, with his familiar smile, faced undaunted the difficulties of starting practice as an eye specialist in London.

Although precluded from surgery because that involves standing unaided, he served three London Eye Hospitals faithfully and well. Throughout the second world war he remained in his London flat, which became a haven of refuge for his many Service friends, and meanwhile he worked harder than ever, ignoring London's wartime discomforts and dangers. The strain of working daily to the limit of his physical endurance, however, could not be maintained indefinitely, and the sad occurrence of a cerebral haemorrhage prematurely terminated this gallant determination to succeed in practice and be independent to the end. Eric Henry is mourned by all who knew him; his cheery generous nature and steadfast courage in adversity will long be remembered.

H. H. S.

BOOK NOTICES

Sight, Light and Efficiency. By H. C. WESTON. Pp. 108, 132 figs. H. K. Lewis and Co. (London). 1949. 42*s*.

The distinguished expert on the general lighting requirements for visual efficiency in industrial occupations has, in this book, registered a powerful appeal for a more intelligent and better informed approach to the visual problems which arise in industry. He points out that none of the specialists concerned with such problems, ranging from the oculist through the job-study and planning expert to the illuminating engineer and factory welfare worker, has, at present, sufficient general knowledge of the factors involved to view this type of problem as a whole, and he has done his best to supply the necessary information.

Most of the visual problems encountered in industry have two sides: the visual equipment of a worker may be deficient in some important respect such as colour vision, visual acuity, or stereoscopic vision; or the task itself may be such as to tax the capacity of the most efficient eye by providing unduly poor contrast or by involving the recognition of very small or rapidly moving objects. It is, therefore, important not only that the visual capacity of the worker should be known and his individual deficiencies corrected if possible, but also that the visual difficulty of the job should be assessed and, as far as possible, minimized. Much can be done by the provision of adequate and suitable lighting, or of visual aids such as magnifying spectacles. In addition, the general lighting provided in factories and workshops can add greatly to the well-being and comfort of those who work in them.

The book is written from an essentially practical point of view, and is full of examples of the way in which attention to such points as sufficient illumination and contrast can increase output and raise morale. Much of the book is based on the author's own observations and experiments both in the factory and the laboratory.

The book is clearly, if not always very interestingly written, and is illustrated by many diagrams as well as by actual photographs of different types of industrial tasks and work places. Unfortunately many of the illustrations, although usually well described in the text, have quite inadequate legends.

Modern Practice in Ophthalmology. By H. B. STALLARD. Pp. 525, 30 coloured plates, 231 figs. Butterworth and Co. (London). 1949. 65*s*.

This book is printed very legibly on good paper and is well illustrated. Great credit must be given to Mr. Stallard for his original drawings. The subject matter is up-to-date and very readable. It

should be noted that St. Margaret's Hospital for Ophthalmia Neonatorum was closed in 1939 at the beginning of the war and has never been re-opened for its former purpose. Minor criticisms are that it might be better to provide explanatory legends for each illustration, mentioning the salient features of the condition appearing in the drawing, and that a few more details about post-operative treatment, particularly regarding the length of time the patient may expect to be warded, would be helpful to general practitioners and house surgeons. These small omissions do not seriously detract, however, from the excellence of the book.

Occupational Eye Diseases and Injuries. By JOSEPH MINTON, F.R.C.S.(Eng). Pp. 184, 24 figs, 3 col. plates. Wm. Heinemann (London). 1949. 21*s*.

Mr. Minton, who has evidently made this subject his own, has produced an eminently readable book of modest size. It deals with a problem which is usually given very little space in the ordinary manuals of diseases of the eye; yet it is obviously of great importance.

The chapters on " Vision and the Selection of Personnel ", " The Employment of the Blind and Partially Blind ", and " The One-eyed Worker " are especially to be recommended. To the House Surgeon one of the great bugbears of eye injuries is the medico-legal aspect. He will find useful guidance in Chapters III and IV. The instructions for the initial treatment of eye injuries are so clear and simple that they can be easily followed by the non-medical first aid worker.

Both author and publisher are to be congratulated on the production of this useful, well illustrated, and well produced guide to those affections of the eye to which factory and other industrial workers are liable.

The Eye and its Diseases. By 92 International Authorities. Edited by CONRAD BERENS, M.D., F.A.C.S., President of the American Academy of Ophthalmology and Otolaryngology. New (2nd) Edition. 1092 pp., 436 figs. W. B. Saunders Company (Phila. and London). 1949. 80*s*.

It seems increasingly difficult with the many advances in the therapeutic field, and with a widening of knowledge in the divers branches of ophthalmology, to envisage a book of reasonable dimensions which will adequately encompass the subject for the student. The new edition of Conrad Berens' book, written as it is by ninety-two authors, must remain subject to the same criticism made in the review of the first edition. It is surely almost impossible to contain within the covers of a single volume the work of

so many eminent authorities, without some contrast of opinion between one section and another. This may be rather confusing to the elementary student, but for those with some experience of ophthalmology, for whom this book is undoubtedly intended, a divergence of views inclines rather to stimulate interest and thought, than to leave the reader bewildered.

The anatomy and development of the eye are covered in less than eighty pages, a difficult task in itself, but the reader is given many references by which he may widen his knowledge. To abbreviate anatomy lays one open to the danger of neglect, and great care has evidently been taken to avoid this possible criticism. Two names, which one might well expect to see, have been omitted from the section on physiology. One has come to associate the name of Fincham with a quite considerable amount of original work on the subject of accommodation, but there is no mention of his contribution to this field. Allowing for some delay between the time of assembling the material and its ultimate publication, especially with a text book, it would seem that at least some of Granit's earlier work on colour vision might have found its place in the chapter on that subject. The section by Traquair on peripheral vision and perimetry is concise, yet comprehensive.

In the extensive section on pathological conditions of the eye and their treatment, Thygeson's chapter on the conjunctiva presents the view that general, rather than local, penicillin therapy is the method of choice in the treatment of ophthalmia neonatorum. This is somewhat misleading in view of Sorsby's work, which suggests that the best mode of application is by frequent local instillations.

It is refreshing, in this world of surgical achievement, to see in the chapter on glaucoma a timely word of warning concerning the ultimate prognosis in cases of the chronic simple variety subjected to operation. A recent review of the results confirms the reviewer's opinion that the outlook is more favourable in those cases which do not " require " operation. The advantages of an operation which gradually lowers the tension are also stressed, and in this connection favourable mention of Herbert's sclerotomy is made.

A wide range of remedies indicates the unfortunate lack of an effective method of treating sympathetic ophthalmitis, but the omission of any anti-biotic from the formidable list is surprising. Medical ophthalmology receives, at first glance, brief recognition. The section under this title rather resembles a descriptive catalogue. Seeking further, however, one finds a chapter on neuro-ophthalmology, which amplifies and considerably extends the space devoted to this important aspect of ophthalmological knowledge.

A curious result of the arrangement of the book is exemplified in the consideration of intra-ocular foreign bodies. The localization and principles of treatment are described by one writer, and another deals with surgical methods of their removal in a later chapter. That bone of contention, the relative merits of anterior and posterior routes for the treatment of magnetic intra-ocular foreign bodies, is kept carefully buried by Comberg. The final chapters on the legal aspects of ophthalmology and on bacteriological technique introduce subjects usually neglected in text books of a similar size and scope.

The entire book is printed in clear and readable type, and is adequately illustrated, both by diagrams and by photographs. One does feel, in looking back through the pages, that more ruthless editing would greatly reduce the duplication of material, some of which appears in more than one chapter in almost identical form. This would appreciably shorten the text, while in no way detracting from the wealth of information provided.

BOOKS RECEIVED

Penicillin; its Practical Application. Edited by ALEXANDER FLEMING. 2nd Edition. Pp. 491, 59 figures. Butterworth and Co. (London). 1950.

A general discussion of abiotic drugs, with a special chapter on their use in ophthalmology. To be reviewed in *Ophthalmic Literature.*

Spectacle Fitting and Optical Dispensing. By L. S. SASIENI. Pp. 294, 241 illustrations. Hammond and Hammond (London). 1950.

A good text-book on the dispensing, fitting, and verification of lenses. To be reviewed in *Ophthalmic Literature.*

NOTES

Meetings. Glasgow

DURING March a series of meetings will be held in the Department of Ophthalmology, University of Glasgow, on Wednesdays at 8 p.m. The general arrangements will be similar to those made for the series held in 1949. A discussion will follow the main paper.

March 1. Dr. D. Christison—"Prognosis in Iridocyclitis"; March 8. Dr. S. Galbraith—"The Evolution of the Ophthalmoscope"; March 15. Dr. J. D. Fraser—"Glioma of the Retina"; March 22. Dr. T. D. M. Roberts—"Primary Visual Receptors"; March 29. Dr. T. Wilson—"Modern Methods of Investigation".

* * * *

Lectures. Manchester and Leeds

DR. RAMON CASTROVIEJO, of New York, is lecturing to the North of England Ophthalmological Society: (1) at the Manchester Royal Infirmary on Thursday, March 30, 1950, at 3.30 p.m.; (2) at the Leeds Medical School on Friday, March 31, 1950, at 3 p.m. All ophthalmic surgeons throughout the United Kingdom are cordially invited to these lectures. In order to facilitate arrangements it is desirable that those wishing to come should communicate with The Hon. Secretary, North of England Ophthalmological Society, 70, Upper Hanover Street, Sheffield, 3.

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New York

THE National Society for the Prevention of Blindness has announced the appointment of Robert S. Krueger as Director of Industrial Service.